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Familial Eunuchoid Gigantism

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THE USUAL classification of giants differentiates between the so-called normal giants and true endocrine giants. The normal giants are tall men, often with tall forebears, with normal sexual development and normal hair growth in whom procreative ability is not known to be impaired. Examples of this type of overgrowth are Falta's (1) giant and Carnera, the boxer. Even in individuals who have been classified as normal giants there are usually the stigmata of hyperpituitarism evident from prognathism, wide spacing of teeth and very large hands and feet. Since, as far as we know at present, growth in length of long bones is dependent upon a stimulus from the anterior lobe of the hypophysis, it is evident that whatever the classification is, abundant or excessive pituitary stimulus must be present in every case of abnormal height.

Familial gigantism has seldom been recorded. Davenport (2) in his studies on inheritance of stature has collected data on a few families with tall members. His conclusions are as follows:

Assuming that excessively tall stature is the result of excessive activity of the pituitary gland, then it seems necessary to conclude that peculiarities in the functioning of endocrine glands are influenced by genetic factors—have an inheritable basis.

Unique in medical history perhaps is the record of the Minneapolis giant, described by Gray (3). His paternal grandfather, the Norwegian giant, was reported to have been 8 ft. 4 in. Both parents were more than 6 feet tall. The giant himself was 7 feet tall. It would appear that the familial and hereditary influence must have been important in this family, also that the disturbance of sexual function must have been only partial. And yet, the picture of the Minneapolis giant is one of advanced hyperpituitarism. The dividing line therefore between so-called normal giants and those due to abnormal pituitary function is at best a vague one.

Pituitary gigantism is considered to be secondary to pituitary tumors. We know that in the closely related acromegaly eosinophilic tumors of the hypophysis have been present in nearly half of the cases which have come to

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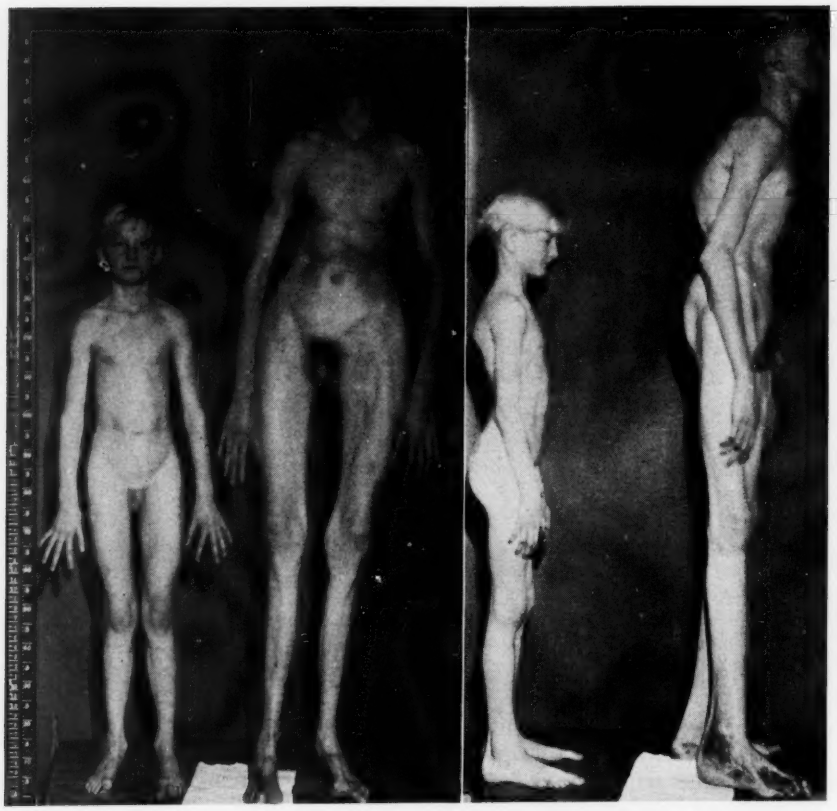

FIG. 1. Brothers, Raymond and Lawrence D., aged 10 and 19 years, respectively. Raymond was 9 inches taller than the average for his age. Note the length of the foot and great toe in photograph on the right. Lawrence was 6 ft. 11 in. tall. Note the size and shape of the hands.

operation or autopsy. Atkinson (4) who collected the cases described from 1935 to 1937 found in 287 cases the occurrence of adenomata in 124 in which the condition of the pituitary gland is reported. It is reasonable to suppose that in gigantism the same may be true in cases which reveal signs of definite hyperpituitarism. The pathologic data on giants are, however, deplorably meager.

The last group are the eunuchoid giants in whom for one reason or another the testes or ovaries develop late or are atrophic or destroyed. The physical status of such patients is very characteristic and consists of absence of secondary sex characteristics, hypotrichosis and impotence, combined with overgrowth of long bones and open epiphyses.

We have had the privilege of studying for several years a patient with typical eunuchoid gigantism.

CASE REPORT

The patient, *Lawrence D.*, was sent to Barnes Hospital from Barnard Skin and Cancer Hospital for study of the etiology and nature of his excessive height. He went to the Barnard Hospital because of an ulcer on his leg, which on admission was still present. The family history will be revealed later. He had the usual children's diseases: measles, mumps, whooping cough and chicken-pox. At the age of 4 or 5 years his unusual height was discovered. When he started to school at the age of 7, no one would believe that he was only 7, but rather thought that he was about 9 ~~nine~~ years old. He was always the tallest boy in his class and far above the average height. He made average marks in school. At the age of 12 years he was 5 ft. 10 in., at 16 he was 6 ft. 1 in., at 18, 6 ft. 5 in., and at the time of admission 6 ft. 11 in. tall.

In 1933 he entered another hospital because of an

undescended left testicle. During his stay in the hospital a kidney infection was discovered and treated. He had never received specific treatment for the undescended testicle, nor for the apparent eunuchoidism which accompanied it. Five months before he entered Barnes Hospital he accidentally struck the inside of his left foot with the shoe of the other foot. Since then there has been an ulcer of the right foot which has caused him to give up his occupation in a printing office, where he was running a press. He never complained of headaches. After long reading he has some blurring of vision. There are no signs of diabetes insipidus. He has very little sexual desire.

Physical examination revealed a very tall young man, 19 years old, whose appearance is best shown by the photograph. The size and shape of the head were normal. There was no evidence of prognathism. The body measurements are shown in table 1. The height was 13.5 inches above the average height for his age. The span was greater than the height. The distance from the pubic bone to the floor was 13.9 inches longer than the sitting height. The hips were broad and the shoulders narrow. He had bowing of the thighs. The pupils reacted promptly to light and accommodation. Eyegrounds and visual fields were normal. The skin was velvety. There was no beard, practically no hair in the axillae and the pubic hair was scant with a female distribution. There was a pronounced dorsolumbar kyphosis. The thyroid gland was of normal size. Examination of heart, lungs and abdomen revealed no abnormalities. The penis was of average size. Both testicles were in the scrotum. The right was of normal size and a little larger than the left one. The lobes of the prostate gland could not be felt. The fingers were very long but not tapering, they were thin throughout their entire length, except for definite thickening of the joints. There was a deformity of the toes of both feet, more prominent on the right foot.[1] Above the right ankle there was an eczematoid dermatitis surrounding a traumatic ulceration. The basal metabolic rate was −7 per cent. The blood Kahn reaction was negative. The blood cholestorol was 139 mg. per cent; phosphorus, 4.1 mg. per cent; calcium, 10.6 mg. per cent. A sugar tolerance test gave the following results in mg. per cent: Fasting, 81; at 0.5 hour, 106; 1 hour, 123; 2 hours, 108; and 3 hours 59. The blood counts were normal. There were no abnormal findings in the urine. Roentgen-ray examination revealed that the skull was symmetrical. The sella turcica was small, shallow and showed some bridging. The sinuses were markedly enlarged. No epiphyseal closure in the bones of the hands and wrists had taken place. There was an extreme kyphosis of the lower dorsal spine, associated with a mild scoliosis, convexity to the right. What were taken to be the bodies of the eighth, ninth and tenth dorsal vertebrae were very poorly defined and appeared to be the site of a destructive process, diagnosed as osteochondritis desiccans juvenilis.

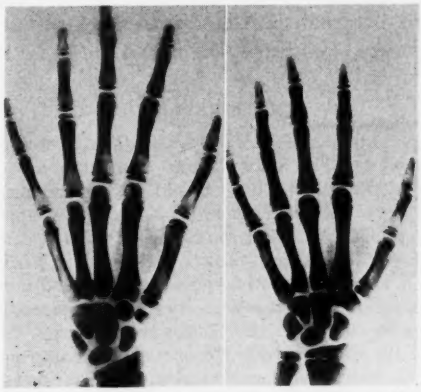

FIG. 2. Roentgen photograph of the hand of ~~Raymond~~ Lawrence (*left*), aged 19 years, and of a male average size and the same age (*right*). The photographs were made simultaneously on the same plate.

TABLE 1. MEASUREMENTS OF LAWRENCE D.

Weight	74.3	kg.	163.5 lb.
Height	2128	mm.	83.0 in.
Pubic bone=floor ht.	1195	mm.	46.6 in.
Span	2080	mm.	81.1 in.
Circumference of			
head	565	mm.	22.0 in.
chest	885	mm.	34.5 in.
abdomen	715	mm.	27.9 in.
Bi-acromial width	355	mm.	13.8 in.
Bi-iliac width	330	mm.	12.9 in.
Left hand length	245	mm.	9.5 in.
Left hand breadth	87	mm.	3.4 in.
Third finger length	110	mm.	4.3 in.
Left foot breadth	108	mm.	4.2 in.
Left foot length	347	mm.	13.5 in.
Great toe length	79	mm.	3.1 in.

TABLE 2. MEASUREMENTS OF RAYMOND D.

Weight	35.5	kg.	78.1 lb.
Height	1586	mm.	61.8 in.
Pubic bone=floor ht.	835	mm.	32.6 in.
Span	1594	mm.	62.2 in.
Circumference of			
head	527	mm.	20.5 in.
chest	620	mm.	24.2 in.
abdomen	570	mm.	22.2 ih.
Bi-acromial width	290	mm.	11.3 in.
Bi-iliac width	225	mm.	8.8 in.
Left hand length	185	mm.	7.2 in.
Left hand breadth	68	mm.	2.6 in.
Third finger length	88	mm.	3.4 in.
Left foot length	281	mm.	10.6 in.
Left foot breadth	82	mm.	3.2 in.
Great toe length	70	mm.	2.7 in.

This case seemed to conform exactly to the classic picture of eunuchoid gigantism. We were, therefore astonished, when our patient brought his youngest brother, aged 10, with him to the clinic, to find the same physical

[1] This he said was acquired by wearing too tight shoes. The toes were unusually long, especially the big toes, and pressed together.

characteristics of skeletal growth, but with apparently normal sexual development.

The family history of the brothers furnished the following data: The relatives on the father's side are all more than 6 feet tall. The father is 6 ft. 4 in. in height, the mother is of medium height. There are 5 children. The oldest is described above. The oldest daughter, 18 years old, is 6 feet tall. She shows no signs of endocrine disturbance. A boy of 16 and a girl of 11 years are of average height and are in no way abnormal

CASE REPORT

The patient's brother, *Raymond D.*, age 10 had no complaints. The past history was irrelevant. He started to walk when one year old. He had had measles and diphtheria. An interesting point about his appearance was the striking resemblance to the descriptions of his oldest brother at the age of 10. He, too, was very tall. The height was 9 in. above the average. The span exceeded the height about $\frac{1}{8}$ in. The distance from the pubic bone to the floor was 3.4 inches longer than the sitting height. He wore shoes of size ten, as did the brother 6 years his senior. The exact measurements are given in table 2. There were no abnormalities of the head and no prognathism. He had long extremities, especially long fingers and toes. Particularly noticeable was extreme enlargement of the big toes. There was symmetrical ankylosis of the metacarpophalangeal joints of both thumbs. The posture was good and there was no deviation of the spine. The pupils reacted promptly to light and accommodation. The thyroid gland was of normal size. Examination of lungs, heart and abdomen showed no abnormalities. The penis and testicles were of normal size corresponding to his age. Both testicles showed normal descensus. Axillary and pubic hair had not developed as yet. The basal metabolic rate was −8 per cent. The blood Kahn reaction was negative. The urine was free from albumin and sugar. Roentgen-ray of the skull showed the sella turcica enlarged and deepened. Neither the dorsum nor the floor had undergone any erosion. The other roentgen studies showed that the ossification centers and epiphyseal lines corresponded to his age. The ankylosis of the thumbs did not affect the bony structure and was apparently a fibrous ankylosis.

DISCUSSION

In previous discussions of eunuchoid gigantism it has been assumed that the abnormal growth was dependent upon failure of sex gland development at puberty, and to this concept the first case, *Lawrence D.*, seemed to conform. In the second case, however, the characteristics were well under way at the age of 10. One of two conclusions seems inevitable, either that the influence of hypogonadism upon skeletal growth may exist before puberty without hypogonadism, or that eunuchoid characteristics may be present, occurring perhaps as an hereditary or familial characteristic.

SUMMARY

The physical status of patients with eunuchoid gigantism is very characteristic and consists of absence of secondary sex characteristics, hypotrichosis and impotence, combined with overgrowth of long bones and open epiphyses. The history of two brothers, 19 and 10 years old, respectively is given. The case of the older boy conforms exactly to the classic picture of eunuchoid gigantism. The younger brother, aged 10, showed the same physical characteristics of skeletal growth, but with apparently normal sexual development. One of two conclusions seems inevitable, either that the influence of hypogonadism upon skeletal growth may exist before puberty without hypogonadism, or that eunuchoid characteristics may be present, occurring perhaps as an hereditary or familial characteristic.

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Ectodermal Disorders in Chronic Hypoparathyroidism

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CHANGES in structures of ectodermal origin in chronic hypoparathyroidism have been described repeatedly. In most cases these disorders were noted as incidental findings of secondary importance. The case which is to be reported presented as a striking part of the clinical picture, skin, hair and nail abnormalities. In addition there were other unusual features.

CASE REPORT

Mrs. M. M., a 50-year old Slovakian woman, was admitted on Dr. C. L. Brown's service on May 18, 1942, complaining of numbness and stiffness of the hands and feet and a recurrent skin disease. She had been in excellent health until 20 years ago, when at the age of 30 she developed difficulty in breathing. Thyroidectomy was advised and done. Following the operation she was relieved of dyspnea, but 5 days later there occurred numbness of the hands and feet accompanied by stiffness in these extremities. These symptoms were relieved by the administration of a calcium salt. On discharge from the hospital she was advised to take one drachm of calcium lactate by mouth 3 times daily. This she did conscientiously, but in spite of the medication she continued to have attacks of tetany as frequently as 4 or 5 times monthly for the next 13 years. In 1935 her family physician advised the use of parathyroid extract by hypodermic at the onset of tetanic symptoms. In the beginning 2 cc. was effective, but as months passed it became necessary to employ increasing doses, and recently as much as 7 cc. has not controlled the tetany.

Several years after thyroidectomy she noted increasing dryness and coarseness of the skin. In January, 1936, she developed a skin eruption involving the chest, lateral aspects of the trunk, the post-auricular areas, and the dorsal surfaces of the forearms. This was at first vesicular, but soon became dry and crusted, and after 2 months disappeared entirely. During these 2 months the episodes of tetany increased in frequency and severity. Following this she remained practically free of symptoms for 2 years, at the end of which time, in January, 1938, the skin lesions recurred, this time associated with moderate loss of hair and complete shedding of the finger and toe nails. With the reappearance of the skin changes, there was an exacerbation of the tetany. During the next 5 months these symptoms persisted, but at the end of that time, in June, 1938, the skin had again cleared and new nails had appeared. Since then, the dermatologic changes, including loss of hair and nails, have recurred each January and have disappeared each June. For the past 3 years tetany has been rare except during those periods when the ectodermal changes are manifest. Four years ago the vision began to fail, and three years ago a left cataract extraction was done.

The diet has been adequate, including cereals, meats, milk, bread, butter, fresh greens, eggs, vegetables and fruit juices. During the winter months the patient rarely ventures outdoors, but in April and May she sits in the sunlight in the garden several hours each day. In the winter she develops fissures in the angles of the mouth which disappear in the summer.

As a young woman she had had swelling and pain in both ankles lasting a few weeks and leaving no residuum. Six years ago a hysterectomy was performed.

Physical examination revealed a large-boned, moderately obese, middle-aged woman lying comfortably in bed. The hair was partially gray, coarse in texture and sparse in some portions of the scalp. The skin of the arms and legs was dry and coarse. Pigmentation and scaling of the dorsal aspects of both forearms were present. All of the nails showed marked changes, particularly at the lunulae. The lunula of each nail was white and crumbly, while distally the entire nail plate was separated and elevated (fig. 1).

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'The lateral aspects of the trunk presented skin lesions remarkable in appearance—solid purplish-red patches sharply marginated from the uninvolved skin (fig. 2). There was thickening of the skin in these patches, and their surfaces were covered with loose flaky scales' (Dr. C. S. Wright). Examination of the eyes by Dr. G. G. Gibson revealed aphakia on the left, the cataract having been removed. An immature cataract was present on the right. This was felt to be of the metabolic type in that there were vacuoles and posterior polar opacities. There were also numerous spicules.

FIG. 1 (*left*). Nail changes, and Trousseau sign on left in case of chronic hypoparathyroidism.
FIG. 2 (*right*). Lateral aspect of trunk of patient with chronic hypoparathyroidism demonstrating the extent and severity of the skin lesion (photographed from above).

Examination of the mouth revealed the presence of angular cheilitis, and a smooth reddened tongue with atrophy of the lingual papillae. Upper and lower false dentures were present. There was a thyroidectomy scar, and a small nodule was palpable to the left of the midline which moved on deglutition. The chest was resonant. A few moist râles were audible at the lung bases. The heart sounds were normal, the rhythm regular, the rate 70 per minute, the blood pressure 128/80 mm. Hg. There was evidence of mild left ventricular enlargement. The abdomen was not remarkable. The deep reflexes were active and equal. Chvostek and Trousseau signs were present. It is noteworthy that as soon as the cuff of the sphygmomanometer was inflated there was marked blanching of the skin of the arm.

Laboratory studies and special examinations. Blood count: red cells, 3.45 million per cu. mm.; hemoglobin, 9 gm., 57 per cent; color index, 0.87; leucocytes, 8000 per cu. mm.; 52 per cent neutrophiles, 36 per cent lymphocytes, 9 per cent monocytes, 3 per cent eosinophiles. Urinalysis disclosed no abnormal findings except for a very slight trace of albumin. Serum calcium 6.8 mg. per cent; serum phosphorus 5.8 mg. per cent; serum protein 6.65 gm. per cent (albumin, 4.76 gm. per cent, globulin 1.89 gm. per cent); serum cholesterol 235 mg. per cent. The Kolmer-Wassermann, Kahn, and Kline tests were negative. The Mosenthal test disclosed normal concentration of the urine. Gastric analysis revealed mild hypo-acidity. The B.M.R. was +5 per cent. The electrocardiogram showed a *Q-T* interval of 0.40 seconds, the heart rate being 96 per minute, the upper limit of normal for this rate being 0.353 seconds (Ashman and Hull). Because of the possibility that the skin and nail changes might have been caused by fungus infection, skin and nail scrapings were examined and cultured. No evidence of fungi was found.

On May 19, therapy was instituted with dihydrotachysterol, 1.25 mg. 3 times daily. This was continued until May 27, the urine being tested 3 times daily with Sulkowitch reagent. (1) A low phosphorus diet was ordered, and one drachm of calcium lactate was given 3 times daily by mouth. The patient also received viosterol, 10 minims twice daily in tomato juice; brewer's yeast, one drachm 3 times daily; and daily intramuscular injections of 50 mg. of thiamin chloride and 100 mg. of nicotinamide. On May 27 the Chvostek and Trousseau signs had disappeared, the serum calcium was 7.7 mg. per cent, the serum phosphorus 7.2 mg. per cent, and the Sulkowitch test revealed a faint white cloud. The patient had had no symptoms for one week. By this time the skin lesions had begun to clear remarkably, although it was not unusual for improvement to occur spontaneously at this time of the year. On May 28 the patient insisted on leaving the hospital. She agreed to remain on the

therapeutic plan outlined, except that the dose of dihydrotachysterol was to be regulated by her family physician depending upon the results of the tests with Sulkowitch reagent.

The patient was not seen again until Nov. 11, 1942, when she returned as an out-patient for check-up. Several days after she had left the hospital the dose of dihydrotachysterol had been reduced to 1.25 mg. daily, and Sulkowitch tests once a week revealed normal levels of urinary calcium. By June 15, 1942, the skin lesions had disappeared entirely, the nails had shed, new nails were appearing, and no further loss of hair had occurred. She had had no tetanic manifestations, and was able to do her housework, had gained 14 lb., and felt better than she had in 20 years. There had been no progression in loss of vision. On examination the pulse rate was 62 per minute, the blood pressure 140/80 mm. Hg. The skin lesions had completely disappeared except for several small light scars. Normal nails were present. The hair was normal in quantity and texture. The scaling on the dorsum of the arms had disappeared. Cheilitis and glossitis were no longer present. The Chvostek and Trousseau signs could not be elicited. There was no blanching of the skin of the arm on inflating the cuff of the sphygmomanometer. The serum calcium was 9.4 mg. per cent; the serum phosphorus 3.4 mg. per cent.

The patient was seen again on March 4, 1943. There had been no recurrence of the ectodermal disorders nor tetany. The serum calcium was 8.9 mg. per cent and the serum phosphorus 1.8 mg. per cent.

COMMENT

The unusual aspects of this case are the marked ectodermal changes, the seasonal recurrence, and the evidences of avitaminosis B which disappeared after the institution of treatment.

'Trophic' changes in tetany are not rare. They involve epithelial parts almost exclusively, particularly nails, hair, skin, tooth enamel and ciliary epithelium. At times tetany may be so mild and the symptoms so transient, that the disease may not be diagnosed, yet these changes may occur (2). As early as 1843 Hearard (3) described shedding of the fingernails in tetany. Since then many cases presenting loss of the nails have been reported (2,4), although most often the only changes noted are brittleness or grooving with or without necrosis of the nail beds. Schelling felt that these nail disorders were probably the result of angiospasm of the of the blood vessels nourishing the nail beds. In this regard it is of interest that our patient demonstrated marked blanching of the skin of the arm below the inflated cuff of a sphygmomanometer.

Coarseness of the hair and loss of hair have been noted (2,4,5,6,7). An acute exacerbation of tetany may be introduced with rapid loss of hair (2). The hair usually returns to normal quantity and texture after the tetany is controlled.

Dryness, roughness, puffiness, thickening and scaling of the skin have been described, (2,4,5, 6,7,), but we are unaware of the occurrence of pronounced marginated skin lesions similar to those reported here. The dermatologic changes too, have been attributed to angiospasm. Pigmentation of the skin is rare.

Cataract formation in chronic tetany is not uncommon (8). Schelling states that until the advent of modern treatment cataracts were more commonly associated with nutritional tetany in young adults and less frequently in parathyroprivic tetany (4). The cataracts are characterized by the subcapsular distribution of the opacities (7). The lens may become a gray–white mass. Lenticular changes may occur with surprising rapidity. One patient developed bilateral cataracts to the point of blindness in the space of 4.5 months (7).

Disturbances in tooth formation are commonly seen in chronic hypoparathyroidism (2, 4, 9, 10). Albright states that when hypoparathyroidism develops before the teeth have entirely formed, one finds aplasia or hypoplasia of the teeth from the point in their development that the disease had its onset (9).

Improvement in the ectodermal disorders with improvement in clinical status is not unusual. Haines (11) noted rapid disappearance of the conditions following treatment, and Cantarow (5, 6) reported two cases of idiopathic hypoparathyroidism in which hair and skin disorders improved after calcium and parathyroid extract therapy had been instituted.

The seasonal recurrence of ectodermal abnormalities accompanied by an increase in frequency and severity of tetanic seizures during the period from January to May is of interest. Exacerbations during the winter months were noted by Schelling (4). Boothby, Haines, and Pemberton (12) noted that a number of

patients with chronic hypoparathyroidism were much better in the summer and early autumn months than in the winter or early spring. In their experience more cases of parathyroid insufficiency following thyroidectomy occurred in the months of January, February, March, October, November, and December, than occurred in the months of April, May, June, July, August and September. They advised their patients to obtain as much sunlight as possible. Swingle and Rhinhold (13) demonstrated that ultraviolet irradiation caused startling improvement in the violent symptoms following parathyroidectomy in dogs. It is recalled that this patient spent much time in the sunlight in the garden beginning in April or May of each year.

The evidences of vitamin B deficiency, namely the glossitis and angular cheilitis, are difficult to explain inasmuch as the patient consistently took a diet rich in the components of the vitamin B complex. It is of interest that cataracts similar to those occurring in parathyroprivic animals and human beings have been produced in rats by the feeding of a diet deficient in the pellagra-preventing factor (14). Schelling (4) has suggested the possibility that those afflicted with nutritional tetany and cataracts also suffer from deficiency in the P-P factor, or that this factor is utilized but poorly by the tetanic or parathyroprivic organism. In some respects the skin lesions in this case resembled those seen in pellagra, except that their distribution was limited largely to the covered parts of the body. In addition, these lesions cleared when the patient was exposed to sunlight, whereas sunlight is known to aggravate the dermatitis of pellagrins. Against pellagra as the basis for the dermatitis was the absence of gastro-intestinal symptoms and characteristic neurologic disturbances.

SUMMARY

A case of chronic postoperative hypoparathyroidism successfully treated with dihydrotachysterol is presented. The unusual features were the changes involving the skin, nails, hair and ciliary epithelium, the remarkable seasonal recurrence of these disorders, and the cheilitis and glossitis which disappeared following therapy.

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Congenital Myxedema Without Mental Retardation

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It is a well-known fact that infantile myxedema, particularly if congenital, is attended by both physical and mental underdevelopment, the latter being characterized by the late appearance or total absence of the successive stages preceding the final mental make-up of the normal child. Such developmental deviation is likely to be accompanied by certain psychic and pathologic disturbances. Mental deficiency, perhaps thyrogenous, in an infant under 10 months of age, is usually betrayed by such signs and symptoms as lack of the sucking reflex, delayed aptitude for holding the head erect, fixing the eyes, recognizing parents and relatives, grasping and playing with objects, turning over, sitting unaided and standing with aid.

Subsequently, the most reliable evidences of mental development will depend on the assimilation of language, walking, control of the sphincters, school progress and mental tests. It should be added here that results of the latter are by no means absolute, much being contingent on personal interpretation and ruling out of all possible misleading factors. Thyroid insufficiency at these ages is consistently manifested as a reduction of general activity; along with changes in emotional balance, behavior, memory and the power of concentration. These changes are variable in degree and in proportion to the degree of the glandular underfunction; they range from very mild disturbances to definite cretinism. The recognition of the milder forms is of prime interest when the real cause is not overlooked and it is to be borne in mind that these minor psychic disorders are met with in the more subtle hypothyroid states. On the other hand, it is exceptional that a full-blown and severe infantile myxedema should not present signs and symptoms of mental impairment. While it is true that quite a variety of symptomatic dissociations may be found both in infantile and adult myxedema—as the endocrine insufficiency is apt to attack some systems or organs more than others—we have not encountered in the medical literature so far any single instance of infantile myxedema without marked mental deterioration. For this reason we are reporting the following case.

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CASE REPORT

J.C.R., male, born in Spain, aged 10 years and 8 months. The chief complaints were underdevelopment, obesity, lack of appetite, constipation, increased thirst and perspiration, sensitiveness to cold, headaches, night terrors, depression, apathy, procrastination and delayed dentition. Growth was about normal until he was 3 years of age at which time there was a slowing which has continued up to the present. The patient weighed 4.5 kg. (9.9 lb.) at birth and 9 kg. (19.8 lb.) at 12 months. The weight at present is 1.5 kg. (3.3 lb.) below the minimum normal for the age, but the patient continues to be adipose because of the marked reduction in stature. Notwithstanding this relative obesity, the appetite has gradually decreased. Relatively frequent vomiting occurred during the first months of life while the infant was still breast fed. Constipation, which has become worse for the past few years, is also stated as beginning in early life. Thirst and perspiration, the latter especially during sleep, were found to be rather increased.

The patient complains of sensitivity to cold more intensely felt on the back of the body. Headaches, severe in type, periodic in occurrence and lasting from 24 to 48 hours, began when he was 5 years old. These are not associated with vomiting but are attended by photophobia and conjunctival congestion. The crises of terrors at night began at the age of 5 also.

The patient is an affectionate boy reported as never being cheerful. He is abnormally quiet and is never excited, even after abusive treatment on the part of

other boys. This is in contrast with the nervous disposition and the propensity to crying which was present up to one and one-half years of age.

Dilatoriness is extreme, but the boy is able to perform a task correctly although slowly. Mental development was normal throughout infancy; holding the head erect, recognition of relatives, walking and talking were normal in the time of their appearance. The sphincters were controlled at the age of 18 months. Apathy began about the third year of life. The intellect is normal at present, if not slightly advanced, according to tests. The patient first became conscious of his shortness in stature about 2 years ago, after other boys made fun of him and called him names; because of this he refused promotion from the third to the fourth grade at school despite being rated as capable.

Personal history. He was born at full term, normally delivered and weighed 4.5 kg. (9.9 lb.) at birth. He was breast fed. There was a right inguinal hernia until he was 8 years of age. As already stated, growth was normal until the child was 3 years old. Both deciduous and permanent dentitions were delayed; the mental development has been good. He had no infectious diseases until the age of 7 at which time he had whooping cough without complications. Rhinitis recurs.

Family history. The mother of the patient, born in Spain, had her first menstruation at 18. She displays a marked apathy and drowsiness. During the pregnancy she gained about 10 kg. (22 lb.).

Physical examination. The patient weighed 25.5 kg. (56.1 lb.; normal for the age, 24–34 kg., 52.8–74.8 lb.). The height was 106 cm. (41.3 in.; normal, 133–142 cm., 51–55 in.), span 105 cm. (40.9 in.); upper measurement, 57 cm. (22.2 in.); lower measurement, 49 cm. (19.1 in.); circumference of the skull, 54 cm. (21 in.); thorax, 60 cm. (23.4 in.); abdomen, 67 cm. (26.1 in.). The height was 27 cm. (10.5 in.) below the minimum normal for the age. The proportion of the body measurements was markedly infantile for the actual age of the patient. The child was plump although the absolute weight was below the minimum normal. The skin was dry, coarse, thick, infiltrated, pale and sallow. There was slight cervical and dorsal lanugal growth. The muscles and bones were somewhat overdeveloped for the small size of the body; the long bones were thick, and the muscles, especially those of the legs were unusually prominent. Lordosis in the lumbar region was conspicuous. The head was relatively large, and the hair dry and thin. There was puffiness of the face; the nose was saddle-shaped. The lips were swollen, the tongue thick and large; there was halitosis. The dentition was markedly delayed; both lower molars, normally appearing at 6, were lacking and only the two upper ones were erupting together with the permanent lower central incisors. The remaining teeth were deciduous. The neck was short and thick, the thyroid was not palpable. There were supraclavicular fat pads. The thorax was thick and adipose. The lungs were normal on auscultation. The heart sounds were normal. The pulse was 80 per minute; the blood pressure, systolic, 90 mm. Hg (it was not possible to determine the diastolic level). The abdomen appeared protuberant, fatty, with tympany. Palpation revealed nothing noteworthy. The genitalia were normal in development for the age. The intelligence quotient, was about 1.13.

Laboratory findings. The results of urinalysis were normal; the blood Wassermann reaction, negative; cholesterol, 265 mg. per cent, blood sugar 115 mg. per cent; blood count: erythrocytes, 3,650,000; Hb., 75 per cent, mean corpuscular volume, 1.02; leukocytes, 8000; neutrophils, 42 per cent; basophils, 1 per cent; monocytes, 1 per cent; lymphocytes, 44 per cent.

Roentgen-ray showed dolichocephaly and the cranial walls to be rather well differentiated, except at the bregma where thinning was present. The sella turcica was enlarged. The sphenoidal and frontal sinuses were lacking. There was a marked osseous retardation of the long bones; the osseous age was 4 years.

Treatment. The patient was given thyroid and has been under observation for nearly 2 years. Striking physical improvement was noted at the end of this time. The height increased 16 cm. (6.2 in.). The proportions changed from infantile toward the normal and the child was no longer obese, although the absolute weight showed a gain of 4 kg. (8.8 lb.). Both the osseous and dental ages were greatly influenced by treatment although they are not yet normal. The skin trouble, as well as the sensitivity to cold, constipation and headaches have vanished. The appetite is better. Beneficial results were also obtained in the activity of the patient. He has now passed the fourth grade at school, but there is no improvement in performance. The mental age, as estimated by the mental tests, remains unchanged, *i.e.*, about 12 years. Ruling out the tests to which the boy may get accustomed, and discounting all possible misleading circumstances related to the repetition of such tests, the mental age of the patient is somewhat above 12, the chronologic age being 12 years and 7 months.

COMMENT

While the actual presence of an infantile myxedema in this patient is beyond doubt, the question arises as to its inception in this particular instance. Relatively accurate inferences can be drawn in this respect from a careful analysis of the personal history of the case. The absence of the molars normally erupting at the age of 6 affords the surmise that the glandular deficiency set in prior to this age. The severe retardation of the osseous age (4 years), together with the small size of the patient for his age and the diminished activity since the age of 3, lead to the assumption that thyroid underfunction began before the child attained the third year of life. Since no patho-

logic condition apt to impair thyroid function occurred during the first few months following birth, it is probable that the disease is congenital in origin. Practically all thyroid deficiencies are congenital which begin before the age of 5, whatever the time of onset between birth and the fifth year of life. Furthermore, evidence is available, first tooth at 1 year (normal, 6th month), early constipation and overweight at birth (4.5 kg.) which points to the patient's having been born with a mild thyroid underfunction which became worse during the first 3 postnatal years and involving chiefly the physical development and affecting only some elements of the mental make-up (emotional activity) while the rest remained normal. The rarity of such a finding in myxedema is the reason for reporting it in a separate paper.

Both psychic and somatic physiologic changes go on uninterruptedly in the young, and the occurrence of a more or less marked degree of failure of the thyroid gland will undoubtedly have an influence both on growth and on mental development. Again, while symptoms of either physical or mental involvement may predominate in some patients showing a dissociated hypothyroid symptomatology, the instance herein reported is unquestionably an exceptional one in thyroid pathology.

SUMMARY

A case of hypothyroidism without mental retardation in a boy, aged 10, is reported.

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Therapy of Seminal Inadequacy I. Use of Pituitary, Chorionic and Equine Gonadotropins[1]

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DURING THE PAST DECADE diverse gonadotropins have been used in the treatment of seminal inadequacy, with varying degrees of success (1–8). Present concepts of male endocrinology, however, lead to expectations of improvement from this therapy only in those patients in whom there is hypogonadotropic pituitary function in conjuction with testes capable of responding to increased gonadotropin levels (9). Therapeutic testing with gonadotropins at present appears to be the only practical clinical expedient for segregating patients likely to be benefited, since no applicable or trustworthy laboratory methods for quantifying pituitary function or testis receptivity are available. This report concerns 21 males with seminal inadequacy whose pretreatment, treatment and posttreatment seminal levels are judged to have been established accurately and whose trials of therapy are regarded as having been well controlled.

METHODS OF STUDY

The diagnosis of impaired seminal function of the 21 males was made during diagnostic surveys of couples made because of sterile mating of 2 or more years' duration. In addition to seminal studies endocrine and urologic surveys were made. All the patients had basal metabolic rate determinations and roentgenograms of the sella turcica. Frequently the levels of urinary 17-ketosteroid excretion were established.

Seminal specimens were studied prior to, during and after therapy. Adequate continence preceded the collection of specimens. All seminal fluid was collected directly and without the use of condoms. Examinations were made within 15 minutes to 1 hour after ejaculation.

The usually accepted criteria for seminal normality were employed: *volume*, 4 cc.; *immediate motility*, 80 to 95 per cent; *minimal count*, 60,000,000 per cc. or 240,000,000 for the entire ejaculate; *normal morphology*, 80 to 95 per cent.

More than one pretreatment seminal specimen was examined in all but 5 instances. Total numbers of specimens per patient varied from 17 to 3, the average being 6.

The therapeutic schedules[3] employed included: pituitary, chorionic and equine gon-

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[2] Parke, Davis and Company Research Fellows in Clinical Endocrinology.

[3] The code numbers (used in the figures and table 1) of the endocrine preparations employed in therapy of these patients and our acknowledgments for the generous supplies of these agents follow: *C-1*, chorionic gonadotropin (APL) by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; *E-1*, equine gonadotropin (Anteron) by the Schering Corp., Bloomfield, N. J.; *E-2*, equine gonadotropin (Gonadogen) by the Upjohn Co., Kalamazoo, Mich.; *T.P.-1*, testosterone propionate (Oreton) by the Schering Corp., Bloomfield, N. J.; *T.P.-2*, testosterone propionate (Perandren) by the Ciba Pharmaceutical Products, Inc., Summit, N. J.; *P-1*, pituitary gonadotropin (Gonadotropic factor) by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; and *P-2*, extract from post-menopausal urine (Gamone) by E. R. Squibb and Sons, New York, N. Y.

adotropins singly; combined therapy with pituitary and chorionic gonadotropins; and combined therapy with equine gonadotropin and testosterone propionate. The usual schedule embraced daily intramusuclar injections for 6 weeks with a rest period of corresponding responses of these patients and additional ones to another gonadotropin preparation (10).

CLINICAL DATA

The ages of the patients ranged from 27 to 43 years. None of them exhibited signs of

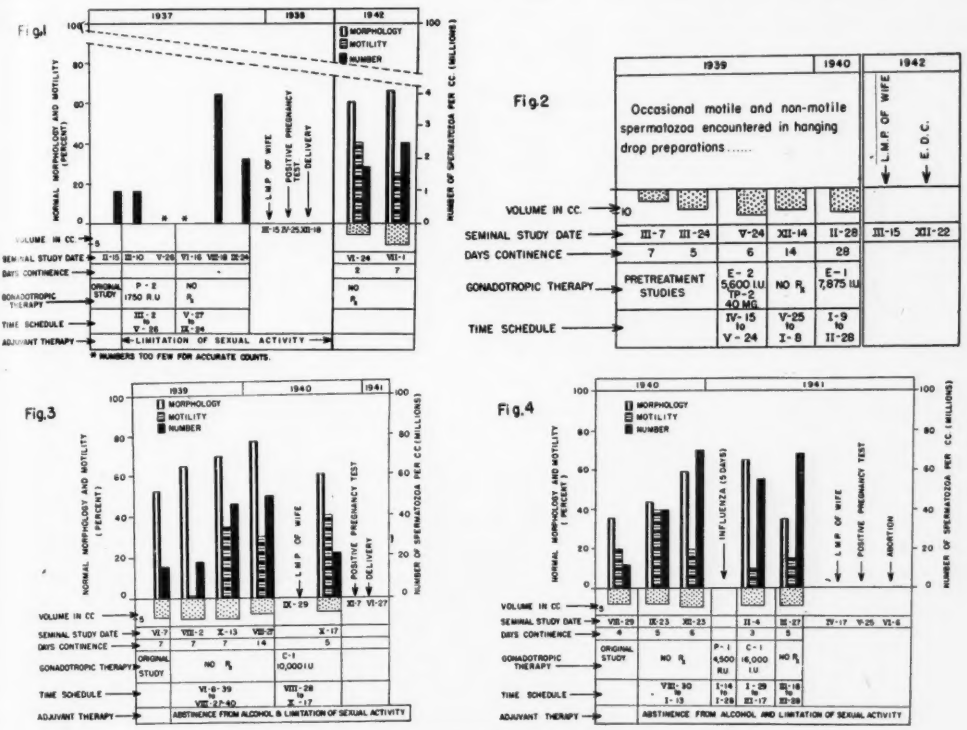

FIG. 1. Clinical data on patient described in *case 1* whose wife became pregnant.
FIG. 2. Clinical data on patient described in *case 3* whose wife became pregnant.
FIG. 3. Clinical data on patient described in *case 5* whose wife became pregnant.
FIG. 4. Clinical data on patient described in *case 8* whose wife became pregnant.

duration before additional treatment was given. The majority of patients received more than one type of gonadotropin and more than one series of treatments.

When hypometabolism made advisable the use of thyroid protein or when hygienic errors or constitutional factors existed, seminal alterations incidental to appropriate adjuvant therapy were assessed before the gonadotropic schedules were initiated.

The periods of observation of our patients varied from 3 months to 5½ years. Six of these patients remain under observation and therapy; a subsequent report will deal with the pituitary or androgenic deficiency. They were classified into 3 groups on the basis of physical findings. *Group I.* Those with normal urologic findings except for seminal inadequacy (*cases 1* to *12*); *Group II.* Those with apparent partial atrophy of one or both testes but with no evidence of androgenic deficits (*cases 13* to *16*); *Group III.* Those with chronic epididymitis and chronic prostatitis (*cases 17* to *21*).

The pertinent clinical data on these 21 patients are summarized in table 1. For analytical purposes averaged seminal levels are reported in terms of total motile spermatozoa (T.M.S. = volume of ejaculate in cc. × im-

mediate motility × number of spermatozoa per cc.) rather than by presenting the four factors of each individual seminal count. These factors for each seminal study of every patient have been plotted graphically and are available for detailed analysis. Figures 1 to 4 give graphically the detailed data for 4 males of *Group I* whose wives became pregnant.

Marked variations characterized values for the different seminal factors of the individual patient. Since these variations were observed to be apparently of the same magnitude prior to therapy as during therapy, they were taken into account in our attempt to assess therapeutic salvage. Table 2 represents the results of analyses for these variabilities in the cases of 12 patients for whom the data were most ample.

TABLE 1. SUMMARY OF CLINICAL DATA OF 21 MALES WITH SEMINAL INADEQUACY

Case Number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pretreatment Values			Average Treatment Values		Average Delayed Post-Treatment Values		Follow-up	
				Number, Sem. Exams.	Total Motile Sperms, Millions	Total Dosage	Number, Sem. Exams.	Total Motile Sperms, Millions	Number, Sem. Exams.	Total Motile Sperms, Millions	Wife Became Pregnant	Further Study and Rx
Group I												
1	38	2		1	(Incomplete data: spermatozoa 1,000,000/c.c.)	P-2, 1,750 R.U.	2	(Incomplete data: spermatozoa 1,000,000/c.c. and T.F.C.)	2	(Incomplete data: spermatozoa 3,000,000/c.c.)	Yes (Fig. 1)	Yes
2	35	3		2	98.5	E-2, 3,600 I.U. E-2, 12,000 I.U.; T.P.-1, 70 mg.	1 2	33.0 100.4	2	41.6	No	No
3	29	2		2	T.F.C.[1]	E-2, 5,600 I.U. T.P.-2, 40 mg. E-1, 7,875 I.U.	1 1	T.F.C. T.F.C.	1	T.F.C.	Yes (Fig. 2)	No
4	34	6		1	0.1	C-1, 18,000 I.U. P-1, 18,000 R.U. C-1, 20,000 I.U.	2 1	T.F.C. (Incomplete data: spermatozoa 2,800,000/c.c.)	1 1	T.F.C. 7.5	No	No
5	42	3½		3	54.8	C-1, 10,000 I.U.	1	32.9			Yes (Fig. 3)	No
6	42	8		3	276.0[2]	C-1, 21,000 I.U.	1	217.0[2]			No	No
7	39	4		2	T.F.C.	P-1, 14,700 R.U. C-1, 18,000 I.U.	2 1	T.F.C. T.F.C.	2 1	T.F.C. T.F.C.	No	Yes
8	34	5		3	47.9	P-1, 4,500 R.U. C-1, 16,000 I.U.	1 1	24.7 45.4			Yes (Fig. 4)	No
9	32	5		3	3.2	C-1, 25,500 I.U.	3	5.1	2	5.6	No	Yes
10	32	4½		2	309.5[3]	C-1, 21,000 I.U.	2	255.0[3]	2	153.5	No	No
11	36	4		2	55.6	C-1, 29,000 I.U.	2	18.0			No	No
12	31	2		3	203.6[4]	C-1, 10,500 I.U.	1	217.5[4]	1	148.7	No	Yes
Group II												
13	30	2	Right testis about ½ normal size. Left somewhat hypertrophied	4	28.6	P-1, 46,000 R.U. C-1, 13,200 I.U. P-1, 13,200 R.U. E-1, 6,750 I.U.	6	53.0	2 2 3	69.0 17.0 19.6	No	Yes
14	27	2	Moderate atrophy of both testes	1	T.F.C.	E-2, 28,800 I.U. C-1, 16,200 I.U.	2 2	T.F.C. T.F.C.	1	T.F.C.	No	No
15	39	6½	Partial atrophy of right testis; orchidopexy 12 years ago	2	0	E-1, 15,750 I.U. C-1, 12,600 I.U. P-1, 12,600 R.U. C-1, 7,200 I.U.	2 1 1	42.0 2.2 0	 2	 3.5	No	No
16	42	11	Partial atrophy of both testes	1	aspermia	P-1, 30,300 R.U. E-2, 6,000 I.U. T.P.-1, 37.5 mg.	2 1	aspermia aspermia	1 1	aspermia aspermia	No	No

TABLE 1. (*Continued*)

Case Number	Age When First Seen, Years	Duration Presumed Sterility, Years	Pertinent Urogenital Findings	Average Pretreatment Values: Number, Sem. Exams.	Average Pretreatment Values: Total Motile Sperms, Millions	Total Dosage	Average Treatment Values: Number, Sem. Exams.	Average Treatment Values: Total Motile Sperms, Millions	Average Delayed Post-Treatment Values: Number, Sem. Exams.	Average Delayed Post-Treatment Values: Total Motile Sperms, Millions	Follow-up: Wife Became Pregnant	Follow-up: Further Study and Rx
Group III												
17	27	5	Chronic prostatitis	3	36.1	P-1, 9,600 R.U.	1	43.7	2	25.3	No	No
18	43	15	Chronic prostatitis. Right epididymis enlarged and thickened	2	T.F.C.	C-1, 6,600 I.U. P-1, 6,000 R.U.	1	aspermia			No	No
19	39	4	Moderate atrophy of left testis. Both epididymides thickened	1	2.8	C-1, 5,400 I.U. P-1, 2,700 R.U. E-1, 15,000 I.U.	1	2.6	1 1	6.3 3.9	No	No
20	32	7	Moderate induration of prostate and both epididymides	2	T.F.C.	P-1, 5,100 R.U.	1	aspermia			No	No
21	30	8	Both epididymides moderately thickened	3	T.F.C.	P-1, 8,700 R.U.	1	1.5	3	40.3	No	Yes

Explanatory Notes:

See footnote 3 under Methods of Study for legends of codes of therapy.

[1] T.F.C. indicates too few spermatozoa to count.

[2,3,4] indicate instances in which the pathological seminal finding, i.e., decreased percentage of normal morphology, which occasioned therapy is not reflected in the formula T.M.S. (total motile spermatozoa): [2] corresponding pretreatment and treatment values for normal morphology in case 6 are 38% and 59%; [3] similarly these pretreatment, treatment and post-treatment values for case 10 are 66%, 57% and 63%; and [4] for case 12 these are 67%, 45% and 66%.

DISCUSSION

Despite reports by other workers of apparent improvements in seminal values incidental to therapy with various gonadotropins, our data provide no evidence that significant enhancements of seminal function were associated with the treatment schedules employed. In view of the fact that our patients are typically representative of male members of childless couples and may be judged to have been at least partly responsible for the sterile mating of these couples and since the various gonadotropins are employed widely in the therapy of these patients, this report seems justified despite the negative results obtained.

We employed chorionic and equine gonadotropins in doses which were as large as, or larger than, those commonly used and which should have been adequate as judged by their ability to evoke specific ovarian responses in the female, and likewise definite increases in the androgen secretion of the testes of adolescent males. The doses of pituitary gonadotropin were admittedly inadequate, due to the low potency of available preparations. Therapeutic schedules were as extended as considerations of antibody formation were deemed to permit. Responses to therapy were sampled by seminal studies during the last week of treatment and after 6 weeks of rest from treatment.

Despite the fact that the patients of *Group I* were thought by their freedom from pertinent urogenital findings to offer the best therapeutic possibilities, only 1 patient (*case 2*, table 1) experienced slight improvement in seminal values during therapy. Two patients of *Group II* (*case 13* and *15*, table 1) and two of *Group III* (*case 17* and *21*, table 1) yielded moderately higher seminal values during treatment

TABLE 2. SUMMARY OF PRE-TREATMENT AND TREATMENT DATA OF PATIENTS WITH SEMINAL INADEQUACY

Gonadotropic Therapy[1]	Group[2]	Semical Factor[3]	I. Average pretreatment values for the indicated groups.	II. Ranges of percentile deviation of average individual pretreatment values from the corresponding ones for the group.	III. Ranges of percentile deviation of single pretreatment values from average individual pretreatment ones.	IV. The percentile deviations of group treatment values from group pre-treatment ones.	V. Ranges of percentile deviation of single treatment values from average individual treatment ones.
Chorionic	I	V	4.7 c.c.	− 58 to + 36	− 20 to + 32	− 9	− 7 to + 7
		C	58,000,000/c.c.	− 72 to +116	− 90 to +145	+ 16	− 96 to + 96
		NM	55%	− 31 to + 22	− 22 to + 29	− 4	− 20 to + 16
		M	37%	− 73 to + 78	−100 to +250	− 6	−100 to +250
	II	V	1.5 c.c.		− 33 to + 33	+ 33	
		C	77,500,000/c.c.		− 45 to + 45	+ 28	
		NM	50%		− 30 to + 40	+ 42	
		M	3%		−100 to +223	−100	
Equine	I	V	6.1 c.c.		− 34 to + 31	− 18	
		C	20,500,000/c.c.		− 61 to + 45	− 47	
		NM	23%		− 65 to + 52	+ 43	
		M	48%		− 75 to + 46	+ 25	
	II	V	3.5 c.c.	− 7 to +166	− 33 to + 33	+ 75	− 33 to + 33
		C	33,600,000/c.c.	− 42 to +171	− 86 to +212	+ 46	− 42 to + 42
		NM	56%	− 10 to + 46	− 60 to + 21	+ 23	− 10 to + 10
		M	40%	−100 to +223	−100 to +223	+ 66	−100 to +100
	III	V	3.6 c.c.		− 30 to + 39	+ 3	
		C	2,900,000/c.c.		− 33 to + 45	− 48	
		M	43%		− 7 to + 16	− 7	
Pituitary	I	V	4.3 c.c.		− 7 to + 16	+ 5	
		C	40,500,000/c.c.		− 70 to + 73	+ 36	
		NM	46%		− 22 to + 29	+ 41	
		M	37%		− 26 to + 48	− 63	
	II	V	4.3 c.c.	+ 11 to + 63	− 16 to + 40	+ 35	− 14 to + 21
		C	15,700,000/c.c.	− 81 to +218	− 86 to +212	+ 15	− 83 to +177
		NM	57%	− 21 to + 3	− 60 to + 21	− 9	− 13 to + 13
		M	54%	− 72 to + 40	− 81 to + 66	− 2	− 71 to + 43
	III	V	4.7 c.c.		− 25 to + 28	+ 6	
		C	23,000,000/c.c.		− 59 to +139	− 24	
		NM	41%		− 52 to + 80	− 49	
		M	40%		− 75 to + 50	+ 25	
Chrionic Pituitary	II	V	1.5 c.c.		− 33 to + 33	+ 33	
		C	77,500,000/c.c.		− 45 to + 55	+ 42	
		NM	50%		− 30 to + 40	+ 52	
		M	3%		−100 to +223	− 66	
Equine Testosterone Propionate	I	V	6.1 c.c.		− 34 to + 31	+ 31	0
		C	20,500,000/c.c.		− 61 to + 45	+ 13	− 5 to + 32
		NM	23%		− 65 to + 52	+ 80	− 30 to +130
		M	48%		− 75 to + 46	+ 4	− 48 to + 56

[1] *Chorionic Gonadotropin:* Group I, 7 patients, 11 series, averaging 6 weeks in duration with an average total dose of 13,000 I.U.; Group II, 1 patient, 1 series, 4 weeks in duration with a total dose of 7,200 I.U. *Equine Gonadotropin:* Group I, 1 patient, 1 series, 6 weeks in duration with a total dose of 3,600 I.U.; Group II, 2 patients, 3 series, averaging 5 weeks in duration with an average total dose of 7,500 I.U.; Group III, 1 patient, 1 series, 8 weeks in duration, with a total dose of 15,000 I.U. *Pituitary Gonadotropin:* Group I, 1 patient, 1 series, 2 weeks in duration with a total dose of 4,500 R.U.; Group II, 1 patient, 3 series, averaging 8 weeks in duration with an average total dosage of 15,200 R.U.; Group III, 1 patient, 1 series, 6 weeks in duration with a total dose of 9,600 R.U. *Chorionic and Pituitary Gonadotropin:* Group II, 1 patient, 1 series, 6 weeks in duration with a total dose of 12,600 I.U. and 12,600 R.U., respectively. *Equine Gonadotropin and Testosterone Propionate:* Group I, 1 patient, 1 series, 9 weeks in duration with a total dose of 12,000 I.U. and 70 mg., respectively.

[2] Group I, II, III: these are the same as previously defined.

[3] Seminal factors: V, volume; C, number of spermatozoa per cc.; NM, normal morphology; M, motility.

but these values were not sustained when treatments were discontinued. The employment of the total number of motile spermatozoa in an ejaculate as a criterion for evaluating therapy appears justified and practical: the foregoing assessments were on this basis. The inclusion of data on morphology in a formula for fertility index, *i.e.*, total number of motile spermatozoa of normal morphology, is impossible at present due to the non-availability of suitable supravital stains.

Of the 5 patients whose seminal values in-

proved during therapy, three had received pituitary gonadotropin and two equine gonadotropin. Reference to table 2 will substantiate the statement that the apparent improvement of these patients might be related to spontaneous fluctuations in seminal values, since the changes observed during therapy were of no greater magnitude than those observed in some patients during pretreatment studies. In no instance were the treatment alterations in seminal values judged to be great enough to warrant the assumption that the fertility of these patients had been significantly enhanced.

Although the wives of 4 of the 12 males of *Group I* ultimately became pregnant, reference to figures 1 to 4 will indicate that it is impossible to correlate these pregnancies with any improvements in seminal values incidental to therapy.

Analysis of our data failed to demonstrate that gonadotropic therapy improves any particular factor studied in the seminal examination, either volume, number of spermatozoa, morphology or immediate motility. Furthermore, there was observed to be no correlation between the degree of seminal impairment and the effectiveness of therapy.

Although subsequent experience with purer, more potent and more completely fractionated pituitary extracts which contain the 'follicle-stimulating' gonadotropin may alter our present views, we are inclined to believe that the cause or causes of seminal inadequacy of this group, and of patients in general, are others than hypogonadotropic pituitary failure. A critical study of the effectiveness of the currently available gonadotropins in the treatment of patients whose seminal failure can be related with certainty to undeniable pituitary disease would provide pertinent information. None of the patients treated by us permitted this diagnosis; indeed, very few husbands with pituitary failure are found in couples who seek medical counsel because of sterile mating.

SUMMARY

Twenty-one male members of childless couples with seminal inadequacy, whose ages (when first seen) ranged from 27 to 43 years and the duration of whose sterile matings ranged from 2 to 15 years, were investigated and treated with various gonadotropins.

Twelve patients presented no signs of andrologic disease; four had partial atrophy of one or both testes; five gave evidence of chronic epididymitis and/or prostatitis. None presented symptoms or signs of pituitary disease or androgenic deficiency.

The following therapeutic schedules were employed: (average series comprised six weeks of daily injections) chorionic gonadotropin, 16 series, average dosage for series 12,600 I.U., pituitary gonadotropin, 11 series, average dosage for series 10,800 R.U., equine gonadotropin, 8 series, average dosage for series 9,700 I.U., and in addition 6 combined series of pituitary and chorionic gonadotropin and 5 combined series of equine gonadotropin and testosterone propionate.

Analysis of treatment data which took into account spontaneous fluctuations of values of various seminal factors, failed to establish any significant enhancement of seminal values relatable to therapy, despite the fact that the wives of 4 patients became pregnant.

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The Physiology of the Endocrines in Pregnancy, Lactation and the Puerperium

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IT WOULD NOT be possible, within the limits of a short review, to survey with any completeness the enormous literature pertaining to the endocrine aspects of pregnancy, lactation and the puerperium. Nor would this be desirable in a review prepared for a journal the primary purpose of which is to present the clinical aspects of endocrinology, chiefly for the benefit of general practitioners. But clinical endocrinology, if it is to be intelligible, must be based upon what is known of the physiology of the endocrines. This paper, therefore, aims merely to summarize some of the more important physiologic contributions of the past few years which have a rather obvious bearing on the interpretation and management of clinical problems in this particular field. Since there is much overlapping in the endocrine aspects of pregnancy, lactation and the puerperium, there would seem to be no advantage, and some disadvantage in separating one from another for purposes of discussion.

The physiologic problems in which, it seems to me, the general practitioner is most likely to be interested are *a*) the hormone rôle of the corpus luteum and the placenta in pregnancy; *b*) the influence of various hormones upon the motility of the uterine musculature; *c*) the probable rôle of the hormones in the initiation of labor; *d*) the endocrines concerned in mammary development and in lactation; and *e*) menstruation and ovulation during lactation. Many other topics suggest themselves, but those mentioned must suffice for a paper of considerate length. In some of these problems important advances have been made in the past few years; in others it cannot be said that a great deal has been added to established facts or to previously accepted theories.

Rôle of corpus luteum and placenta in pregnancy. The numerous studies of the past few years have apparently established the sequence of the rôle of the corpus luteum of pregnancy and the placental trophoblast in the production of progesterone. Moreover, the work of Browne, Venning and Henry (1, 2) indicates that, on the basis of studies of pregnanediol excretion, the placenta takes over the chief burden of progesterone production from the corpus luteum at a comparatively early stage of pregnancy, from the late second to the third month. On the other hand, Cope (3) has recently called attention to certain limitations in the interpretation of pregnanediol excretion, urging that the output may possibly reflect the state of the endometrium in early pregnancy more than the activity of the corpus luteum. He believes that the pregnanediol excreted probably represents only a small proportion of the endogenous progesterone, although qualitatively it is an index of corpus luteum activity in either the pregnant or non-pregnant woman. It will be recalled that Hamblen and his co-workers (4) have long stressed the probable rôle of the endometrium in the fate of progesterone, and Cope calls attention to the discrepancy between the relatively large amounts of pregnanediol recovered after progesterone injection by Venning and Browne (1, 2) and the failure to recover any of the excretion product by Hamblen, Ashley and Baptist (4, 5), as well as by Stover and Pratt (6). Cope's own results were intermediate between these extremes, and he suggests that unknown factors other than the

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endometrium may be involved. If this applies to injected progesterone, it is probably true also of endogenous progesterone.

That the corpus luteum hormone is essential to the maintenance of early pregnancy in some animals, such as the rabbit and rat, has been well established. Moreover, Allen and Corner (7) showed that even after early ablation of the ovaries in pregnant rabbits the administration of progesterone will permit pregnancy to continue to term. In other animals, including the primates, the rôle of the corpus luteum is now known to be not nearly so important. In monkeys, Hartman (8) has shown that pregnancy may proceed to term after early removal of the corpus luteum, and there have been many reports in which human pregnancy was not disturbed by early removal of the corpus. This is not equivalent to saying that the corpus luteum hormone is of no importance, for such is not the case, and abortion is not infrequently the result of early removal of the yellow body. The indication, however, is that the production of progesterone may be taken over very early in trophoblastic development. The bearing of this question on the treatment of threatened miscarriage and repeated abortion is manifest, but this will be discussed later.

Influence of hormones on uterine motility. This subject has provoked innumerable studies during recent years, and the results of these are brought together in the recently published book of Reynolds (9). There is almost general agreement that the spontaneous rhythmic contractility of the uterine musculature is dependent upon the follicular hormone, while progesterone is an inhibitant of this contractility. From this standpoint the myometrium, therefore, exhibits a definite physiologic cycle paralleling the cycle of the endometrium. On the other hand, a number of workers are in disagreement with these views: Kurzrok, Wiesbader, Mulinos and Watson (10), Wilson and Kurzrok (11), Wilson (12) and Moir (13). For example, the group represented by Wilson and Kurzrok assert that even though, as Knaus (14), Robson (15) and Reynolds believe, the uterus of the rabbit remains quiescent in pregnancy under the influence of progesterone, this is not true of the human uterus. These investigators find that during the follicular phase of the cycle, contractions are of small amplitude and short duration, and during the luteal phase they increase in amplitude and duration, while decreasing in frequency and tonus. During pregnancy, Wilson (12) finds that the human uterus normally contracts in a totally arrhythmic fashion. It should be remembered, however, that during pregnancy another factor becomes operative, that of uterine distention, and Reynolds (9) believes that this has a profound effect upon the contractility of that organ.

This author sharply criticizes the technique employed in the experiments of Kurzrok and his associates, as well as those of Krohn, Lackner and Soskin (16), and his own studies have led him to believe in the correctness of Knaus' belief that progesterone is an inhibitor of uterine motility during pregnancy. It is difficult for the clinician to evaluate these differing viewpoints intelligently for himself, based as they are upon technical laboratory methods. It is fair to state, however, that the evidence and opinion of most investigators points to the probable correctness of the viewpoint of Knaus and Reynolds.

This question is not without importance in clinical practice, as the assumed quieting effect of progesterone upon uterine motility constitutes at least one reason why this substance has achieved wide vogue in the treatment of threatened miscarriage. There are innumerable clinical reports in the literature indicating its value for this purpose, although many of them are uncritical and of little scientific value.

As was pointed out in a recent paper by the present author (17), the difficulty in interpreting results lies in the absence of satisfactory controls. The occurrence of uterine bleeding has been the chief criterion in the assumption of threatened abortion, but the significance of this symptom is quite variable, and in a large proportion of cases miscarriage does not occur even when no hormone therapy of any kind is employed; hence the benefits of progesterone, when its use is resorted to, are difficult to evaluate. This comment is not a criticism of such treatment, which is rational not only from the standpoint of its effect upon the uterine musculature but for other reasons as well, but it is a criticism of the conclusions drawn by many authors as to percentages of success in

the treatment of threatened abortion. This paper is not meant to deal with the therapeutic aspects of the endocrinology of pregnancy, but the above clinical digression will serve to indicate the practical bearing of physiology upon the treatment of certain pregnancy disorders.

Another clinical problem bearing on the possible influence of hormones on musculature concerns the urinary tract. Hundley and his coworkers (18) have presented evidence which they believe indicates that the dilatation of the ureters seen so often in the late stages of pregnancy may be due to the relaxing action of progesterone upon the smooth muscle. On the other hand, Payne and Hodes (19) were not able in their experiments on dogs to produce ureteral changes demonstrable by intravenous pyelography, especially dilatation, by means of injections of estrogen, progesterone or chorionic hormones. The studies of Brack and Langworthy (20) on rats confirm those of Woolsey and Brooks (21) that the increased capacity of the bladder which they had repeatedly noted in pregnant animals is due to decreased tone, and that progesterone is the hormone probably concerned in bringing this about.

Probable rôle of hormones in initiation of labor. The bearing of this question of hormonal control of uterine motility upon the problem of the initiation of labor is evident. The determining forces in parturition would seem to be *a*) removal of certain inhibiting factors or *b*) the addition of certain positive factors promoting expulsive contractions, or *c*) both. Of the first group, progesterone would seem to be most important. Of the second group, the follicular hormone and the oxytocic principle of the posterior pituitary have suggested themselves to many workers. Robson (22) had suggested that the cause of parturition was to be sought in the gradually increasing sensitivity of the uterine muscle to the posterior pituitary hormone, as a result of the steadily increasing amount of estrogenic hormone. On the other hand, Heckel and Allen (23) have shown that in the rabbit parturition is delayed by the continued injection of estrogen in the latter part of pregnancy. They find, also, that under these conditions the corpora lutea are maintained and their continued activity is responsible for the delay in parturition. Their experiments lead them to conclude that labor occurs because of retrogression of the corpora. These authors suggest that the aging process in the placenta which makes it unable to continue the production of estrogen is a possible cause of the decline of estrogen, responsible for the waning of corpus luteum activity. It will be recalled that one of the old theories of pre-hormone days attributed the onset of labor to the increasing ischemia resulting from increasing sclerosis of the placental vessels toward the end of gestation.

Rôle of hormones in mammary development and lactation. Since the discovery of the lactogenic hormone by Stricker and Grueter (24), in 1929, an enormous amount of investigation has been devoted to the problem of lactation. While it is universally agreed that this hormone plays an essential part in the phenomenon, the exact mechanism is still far from clear. With regard to the growth of the mammary glands during pregnancy, there is general agreement that the ovarian hormones are responsible. Estrogen has been believed to furnish the hormonal stimulus for the proliferative growth of the duct system, and progesterone for the acinar and lobular development of the breast tissue. However, the mechanism is probably not so simple as this. For example, Selye (25) has reported that in rats progesterone alone, if given in sufficiently large doses, can produce complete mammary growth. Furthermore, Gomez and Turner (26) have shown that neither estrogen alone nor estrogen plus progestin will stimulate mammary growth in the hypophysectomized rat, while anterior pituitary material does induce both duct and lobule-alveolar growth in such an animal. They therefore postulate a pituitary-mammogen theory of mammary-gland growth, according to which 'estrogen stimulates an increased secretion by the anterior pituitary of a duct-growth factor, while progestin plus estrogen causes an increased secretion of a lobule-alveolar growth factor by the pituitary' (27).

The chief discussion of recent years has revolved about the question of why lactation does not occur during pregnancy, and what the factors are which initiate it several days after parturition. As Turner and Meites say, four views have been offered by way of explanation: *a*) the placenta produces a suppressing agent

during pregnancy which holds lactation in check; *b*) the mechanical distention of the uterus by the fetus and placenta inhibits lactation; *c*) the secretion of progesterone by the corpora lutea suppresses lactation during pregnancy; and *d*) during pregnancy the comparatively large amounts of estrogen present in the blood stream inhibit the lactation process.

Until the past few years the theory which was apparently most favored, and is still held by many, was that suggested in 1936 by Nelson (28), who believed that during pregnancy estrogen inhibited the secretion of lactogen by the pituitary and that it also exerted an inhibiting effect upon the mammary gland. However, Turner and Meites (29), point out that this theory does not explain the occurrence of simultaneous pregnancy and lactation in certain species, nor does it explain the fact that the augmentation of the lactogen content in the pituitary by estrogen injections is experimentally possible in certain species. Their own studies have shown that the lactogen content of the pituitary remains low throughout pregnancy, but increases from 2 to 4-fold following parturition. These findings indicate, they believe, that lactation fails to occur during pregnancy for the reason that the lactogenic hormone is inadequate to support lactation. Some as yet unknown factor is responsible for the increased production of lactogen after parturition.

As evidence to support his theory of lactation, Nelson had shown that large doses of estrogen are apparently capable of inhibiting lactation in guinea pigs, at least for a time. Other authors had reported similar results for other animals: Parkes and Bellerby (30), Robson (22), Reece and Turner (31), Folley and Kon (32). Moreover, many reports have been made by clinicians of inhibition of lactation by the administration of estrogenic preparations, especially stilbestrol, as well as with androgens: Foss and Phillips (33), Kurzrok and O'Connel (34), Clahr (35), Diddle and Keettel (36), Stewart and Pratt (37), and others. On the other hand, Smith and Smith (38) noted no significant effect on lactation following the administration of 4000 R. U. of estrogen for 6 days.

Meites and Turner likewise question the validity of reported observations upon the human female tending to indicate inhibition of lactation by estrogens or androgens, one obvious objection being that the infants were taken from the breasts when such therapy was begun, this in itself furnishing an adequate explanation of cessation of milk production. As further evidence along this line Abarbanel and Goodfriend (39) and later Abarbanel and Klein (40) found that when suckling was permitted to continue, lactation was not prevented by stilbestrol in doses as high as 500 mg. If even larger amounts, as much as 1000 mg., were given in divided doses, beginning soon after parturition, lactation was not prevented, although it might be delayed for from 2 to 6 days after the last dose of stilbestrol. Similar ineffectiveness for even very large amounts of testosterone propionate, methyl testosterone, anhydro-oxyprogesterone and progesterone have likewise been reported by Abarbanel.

The issue which is apparently involved in this aspect of the problem of lactation would seem to be whether large doses of estrogens or androgens can suppress the lactogenic hormone, as had been suggested by Nelson, and further studies on this point have been reported in the above mentioned paper of Meites and Turner (41). The experiments were made with rats. Large dosages (2 mg. daily) of stilbestrol or testosterone to lactating rats for the first 6 days post partum not only did not decrease the lactogen content in the pituitary, but actually increased it, although some reduction in the amount of milk present in the mammary gland was noted. Incidentally, parturient rats which were not suckled for the first week showed 50 per cent less lactogen in the pituitaries than suckled rats, and the mammary glands were practically devoid of milk. This observation, so in accord with every-day obstetrical experience, throws a revealing light upon clinical reports as to the value of stilbestrol in the inhibition of lactation when the babies are simultaneously taken from the breast.

In another paper Meites and Turner (42) attacked the problem of why the lactogen content of the pituitary is relatively low when the estrogen production is at a high level. Their experiments showed that suitable combinations

of progesterone and estrogen 'either entirely prevented or reduced the increase in lactogenic hormone which could be obtained with estrone alone.' They believe that the lactogen content remains as low in the pregnant as in the non-pregnant state because this progesterone-estrone ratio overrides the lactogen-stimulating effects of estrone. In other words, the deficiency of lactogen explains the lactation inadequacy.

In view of the numerous reports now appearing as to the use of estrogen in the inhibition of lactation and, more particularly in the relief of so-called painful engorgement of the breast, there may be some confusion in the minds of practitioners, in view of what has been said above. This confusion is resolved if one remembers that a sharp distinction is to be drawn between painful engorgement of the breast and the onset of lactation. As Abarbanel and Goodfriend (39) remark, 'most of the clinical reports on the effects of estrogens upon lactation in the human have confused painful engorgement with the onset of lactation.' As regards the former of these, clinical reports agree that estrogens and androgens are effective in its relief. Abarbanel and Klein (40), for example, report that stilbestrol in doses of 25 to 40 mg. prevented painful engorgement in 87.3 per cent of 55 non-nursing mothers. In 20 of these some transitory heaviness, usually painless, was noted in 20 cases on the 5th to the 11th postpartum days. They stress the fact that pregnant and puerperal women are extremely tolerant to stilbestrol, large doses of from 250 mg. a day to 1500 mg. a week producing no harmful effects, nor does there appear to be any toxic effect even in eclampsia or fulminating toxemia. Other authors who have reported good results with the estrogenic therapy of painful engorgement are Diddle and Keettel (36), Beilly and Solomon (43) and Stewart and Pratt (37).

While there is still much to be learned as to the factors responsible for the initiation of lactation, there appears to be a much closer approach to general agreement as to those concerned in its continuance. Selye and his coworkers (44) had shown in 1934 that the nervous stimulus of suckling was an important factor in the maintenance of lactation, once it has been begun, and they offered as the probable explanation for the mechanism that this stimulus brings about an increase in the lactogen of the pituitary. The act of suckling does not appear to be essential for the initiation of lactation, its importance being rather in the later maintenance of that function. This at any rate applies to rabbits, which were used in the recently published study of Meites and Turner (45). In this animal it was found that even in the initiation of lactation, the act of nursing plays some part in that 'maximum lactation and maximum lactogen in the pituitary cannot be obtained without it. Furthermore, in the absence of nursing after parturition, the lactogen content of the pituitary declines rapidly and milk secretion soon ceased. This observation in a lower species conforms with the everyday clinical experience of obstetricians with human lactation.

Menstruation and ovulation during lactation. During the past year there have been several efforts at study of the much neglected question of the effect of lactation upon menstruation and ovulation. The fact that pregnancy not infrequently occurs during the amenorrhea of lactation has generally been rather complacently explained by the statement that ovulation occurs in the absence of menstruation. Such a belief is difficult to reconcile with what we know as to the sequence of ovulation, corpus luteum maturation and later regression, and then menstrual bleeding. It has therefore seemed more likely that the occurrence of pregnancy during lactation amenorrhea indicates merely fertilization of an egg from a first ovulation, and that if the fertilization had not supervened the ovulation would have been followed by menstruation.

Support has been given to this belief by the recently published study of Topkins (46), based on endometrial biopsies during the period of lactation. The study included 145 biopsies from 28 women, at least 4 biopsy specimens being obtained from each woman, including the time span between 6 and 31 weeks post partum.

Of the 145 specimens, 136 (94 per cent) showed an estrogenic endometrium, and 20 of these (15 per cent) showed evidence of hypoplasia. In only 9 specimens (6 per cent) were progestational changes found, and all of these were associated with the onset of the first men-

strual period. The author concludes that 'the endometrium during the period of lactation amenorrhea is similar to that found in amenorrhea caused by other factors; it shows diminished estrogenic stimulation.' He believes that the suppression of the cycle in women with lactation amenorrhea is complete, while in those who menstruate it is incomplete. This latter statement agrees with the findings of Lass, Smelser and Kurzrok (47), published in 1938, and based on the study of biopsies on 47 women through the postpartum period. These women exhibited 194 fairly regular cycles, of which 106 (55 per cent) were anovulatory or sterile in character, while 82 (45 per cent) cycles were ovulatory in character. Finally, reference may be made also to the report of Griffith and McBride (48) in 1939, who in a study of endometrial biopsies in 21 normal lactating women at intervals of from 3 to 24 weeks post partum found that only one woman had ovulated prior to the re-establishment of menstruation.

The hormonal mechanism by which the cycle is inhibited during lactation is still a matter of conjecture, as Topkin discusses in his paper. The immediate factor is undoubtedly a suppression of the pituitary gonadotropin, but whether this is due to the lactogenic hormone or to some as yet unknown internal secretion of the lactating breast cannot be stated.

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Endocrine Tumors of the Ovary

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THAT OVARIAN TUMORS may exert definite and profound effects upon the female organism as a whole has long been known. As early as 1905 (a), Pick called attention to a tumor which he called tubular testicular adenoma, associated with masculinization in a young girl. Since that time other tumors of the ovary have been described which manifest hormonal effects such as feminization, masculinization or other changes, and which have proved of the greatest interest not only to the gynecologist but to every physician. The field which has thus been opened is still under intensive investigation, and although considerable advances have been made, much remains to be done. The clarification of the subject is to a great extent due to the studies of Meyer (1918–1932) who was the first to offer a definitive classification of ovarian tumors in which the endocrine effects were stressed. The difficulties heretofore encountered in the recognition and the correct classification of the tumors, it would appear, have been primarily due to the fact that the studies made were almost entirely along morphologic lines. The advent of improved methods for the isolation and titration of the hormones elaborated by the neoplasms has served not only to prove their endocrine nature, but also to allow for their proper classification. It is to be emphasized that hormonol and chemical investigations offer the greatest hope for a better understanding of the entire subject. It is our conviction that as a result of such studies therapy in the future will be modified to a great degree.

In order to understand the origins of the endocrine neoplasms a consideration of the embryology of the ovary becomes essential.

In the early embryo the celomic epithelium on its mesial aspect anterior to the mesonephros is seen to proliferate giving rise to a structure in which the cells are high and many-layered. This area is the site of the future genital gland, and in the early stage is undifferentiated showing neither masculine nor feminine gonadal characteristics. In the 5.3 to 7 mm. embryo the cells of the surface layer of the future gonad increase rapidly by mitosis, apparently invade the underlying mesenchyme, and form masses of solid cell cords. At this stage the indifferent sex gland consists of a layer of superficial epithelium, the radially arranged cell cords and a connective tissue framework probably derived from the mesenchyme. This structure is known as the epithelial nucleus. Primitive germ cells now make their appearance both in the surface epithelium and the epithelial nucleus. Their origin is obscure and for the purposes of this paper their development need not be discussed. The origin of the cell cords of the epithelial nucleus is still the source of considerable controversy since many authors, notably Fischel (1929, 1930) believe that they arise from a metamorphosis of the embryonal mesenchyme while others (Goodall, 1919) trace their genesis to the surface epithelium. The point of view taken here is important since it bears a direct relationship to the tumors to be discussed. Transformation into the definite sex gland quickly follows the indifferent stage. After the third fetal month a connective tissue growth appears which replaces many of the cells of the epithelial nucleus and a new epithelial nucleus is formed. Part of this structure now projects into the region of the mesovarium forming the rete ovarii which is surrounded by connective tissue radiating into the sex gland in the form of cords known as rete cords. These usually disappear but may persist into adult life. The cell cords of the epithelial nucleus in the male form the tubular system while in the female they become the granulosa and theca interna cells. Sections of the gland undergoing differentiation show masses of 'eggballs,' stroma, early ova, genitaloid cells, and surface epithelium (fig. 1). In the final stages there is further proliferation of connective tissue with a resulting differentiation into cortex and medulla, and the isola-

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tion of the primordial graafian follicles either as single entities or arranged in groups. It can readily be seen that the complicated processes involved in this growth and development bear a definite relationship to the tumors of the ovary which appear in later life.

The endocrine neoplams of the ovary may conveniently be divided into 3 groups: tumors producing feminizing effects; tumors producing masculinizing effects; tumors producing other effects.

Tumors Producing Feminizing Effects

These are 2 in number, the granulosa cell tumor, and the theca cell tumor. Although the effects they produce on the female organism are similar, there are certain distinct differences, especially from the point of view of morphology which makes it necessary to discuss them separately.

Granulosa cell tumor. This tumor was first described more than 50 years ago, but its true nature was not recognized until recently. It was at first believed to arise from the primordial follicle because it apparently contained ova-like inclusions in carcinomatous tissue. It was therefore called 'adenoma carcinomatosis folliculare,' (Kahlden 1895), 'adenoma folliculare ovarii' and folliculoma until Liepman showed that the inclusions were not ova but cell secretions or degenerated cells. Schmincke (1914) pointed out the similarity between the cell arrangement of the tumor structure and the cell arrangement of the granulosa cells about the graafian follicle, and Meyer (1918) suggested its origin from the primitive forerunner of the granulosa cells found in the adult graafian follicle. It was accordingly named 'granulosa cell tumor' (V. Werdt 1914). The neoplasm probably has its origin from the cells found in the epithelial nucleus in the primitive gonad which have remained in a state of arrested development, but which would have become the granulosa cells of the follicular apparatus had development proceeded normally.

Pathologically, the granulosa cell tumor is usually unilateral, occurring bilaterally in only 10 per cent of cases. It varies in size from a few millimeters in diameter to twice the size of an adult's head. It is encapsulated, its surface is smooth, usually lobulated, and although solid in consistency may contain cysts. It is sessile, and if pedunculated may undergo torsion. On section it presents a medullary, cellular, yellowish cut surface, with connective tissue bundles traversing the tumor irregularly, resulting in a lobular appearance. When cysts are present they contain a fluid which varies from one that is thin and straw-colored to one that is thickly mucinous or gelatinous. Hemorrhage into the tumor or cysts may occur resulting in necrosis. As seen under the microscope 3 types may be distinguished: the folliculoid, the cylindroid and the sarcomatous.

The folliculoid type, as the name would imply, resembles the follicle seen in the normal ovary (fig. 2). It is composed of round or polygonal cells, closely packed together and showing central vesicular nuclei. Due to the distribution of connective tissue, varying-sized compact masses, the cells of which often have mitoses, are formed. In the center of the cell mass a small cavity is seen and this usually contains one or more degenerating cells resulting in a resemblance to an ovum. The radial arrangement of the granulosa cells about this cavity makes the resemblance quite striking.

The cylindroid type is also composed of granulosa cells, but these are usually cuboidal in shape (fig. 3). The cells are divided into columns or cords by fine connective tissue strands and within the cord spaces a cellular or connective tissue debris can be seen. The arrangement may be quite irregular so as to give a bizarre appearance; cell cords, connective tissue and cystic spaces intermingling freely. The connective tissue may become hyalinized.

The sarcomatous type of granulosa cell tumor is composed of plump, closely packed spindle cells resembling a highly cellular fibroma. There are large areas of connective tissue and this results in a sarcomatous appearance. However, within the meshes of the connective tissue, collections of granulosa cells can usually be distinguished.

In all 3 types cyst formation may occur due to degeneration of the cells with secretion of fluid which may reach considerable quantities. The epithelial lining of these cysts, when present, is usually low cuboidal in type. Although the cyst fluid may contain the estrogenic hor-

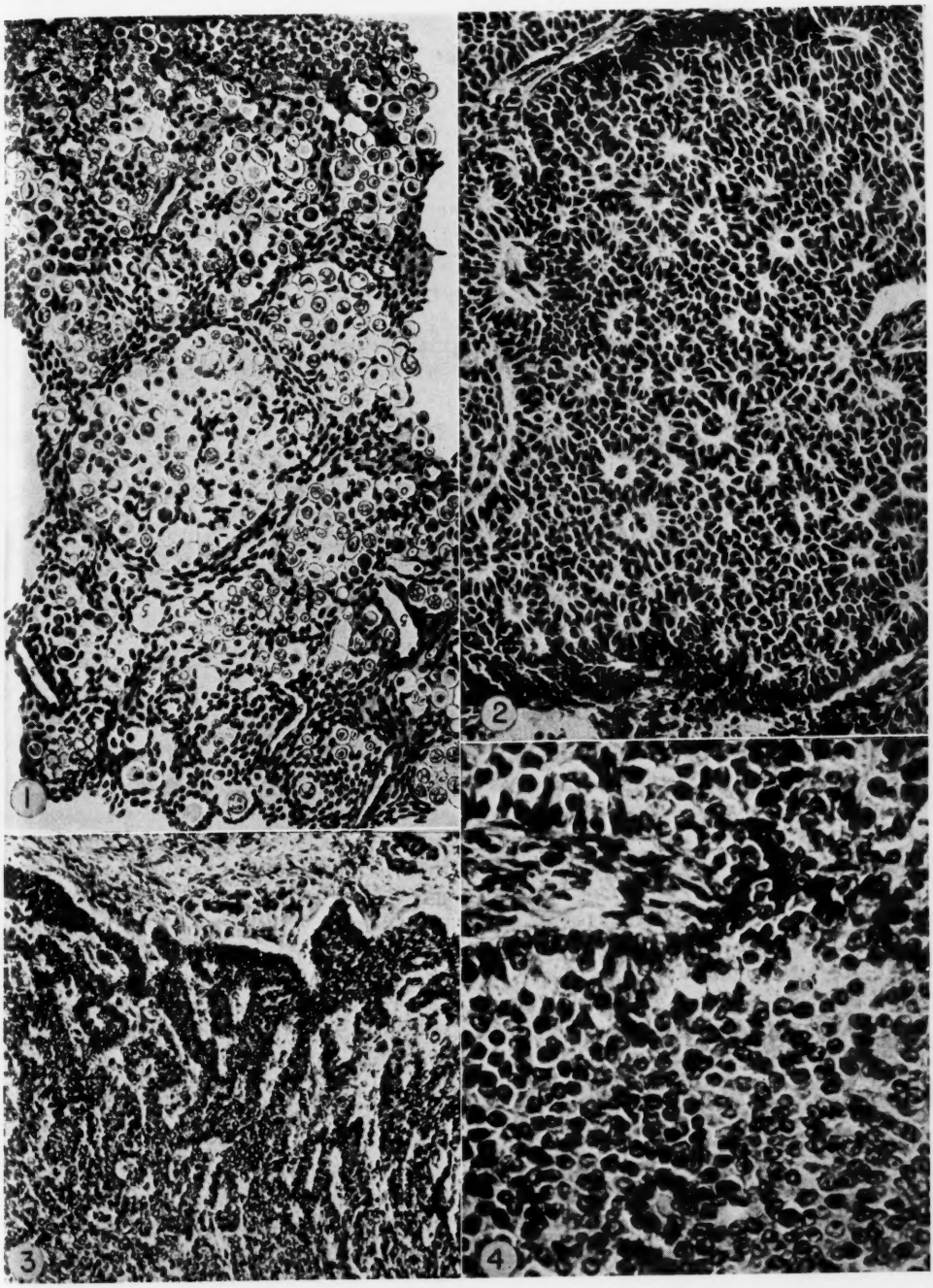


FIG. 1. Medium power. Differentiated gland with parenchyma showing 'egg balls,' stroma, ova, genitaloid cells, and surface epithelium. (From Lubarsch: In Halban and Seitz: Biologie und Pathologie des Weibes. Berlin, Urban, 1929.)

FIG. 2. Low power. Folliculoid granulosa cell tumor.

FIG. 3. Low power. Cylindromatous granulosa cell tumor.

FIG. 4. High power. Malignant granulosa cell tumor with rosette formation and mitoses.

mone in large quantities, the hormone is more likely to be found in the extract of the solid tissue. It has repeatedly been isolated from the tissue cells (Meyer (1930 c), Klaften 1932, 1933; Neumann 1933). Lipoid, chiefly cholesterol and cholesterol esters, is also seen in both the cells and the connective tissue.

Clinically, the most striking feature associated with the granulosa cell tumor is its feminizing effect upon the individual. Since it has been described at all ages (from 3½ to 70 years) it is interesting to note that the effects do not vary. In children, signs of precocious puberty appear, *i.e.*, enlargement of the breasts and the external genitalia, precocious menstruation, the development of axillary and pubic hair, and even colostrum secretion in the breasts. In the mature female before the menopause, since there is already a sufficient quantity of estrogenic hormone in the system, the effect is accentuation of the sexual characteristics as evidenced by an increase in uterine bleeding to the point of menometrorrhagia, and enlargement of the breasts. The uterus enlarges slightly and the endometrium presents the picture of typical hyperplasia even to the formation of polyps. In women past the menopause there is a recurrence of bleeding usually irregularly prolonged in character, an increase in the size of the breasts, and a return of the uterus and vagina to the mature, child-bearing state. It is evident that all of these changes are brought about by the estrogenic hormone elaborated by the tumor. As further proof, the regression of all the symptoms and signs mentioned after the removal of the tumor, is stressed.

The neoplasm may be benign or malignant (fig. 4). If malignant, the presence of metastases or recurrences after extirpation of the primary growth is accompanied by a recurrence of the symptoms already described.

Treatment consists in removal of the tumors by operation. If benign and unilateral, the second ovary and the uterus in the young individual is to be left intact. In this type the tumor is usually freely-movable, sessile, and there is no evidence of ascites, adhesions, or peritoneal implants. If malignant, both ovaries should be removed, preferably with hysterectomy. This also applies to women in the postmenopausal period. Radiotherapy in malignant cases has been reported as a valuable aid when administered after operation.

It may be mentioned here that unusual forms of 'granulosa cell tumor' have been described which are accompanied not by feminizing effects but by masculinization. These neoplasms are discussed later on.

Theca cell tumor. The second of the feminizing tumors of the ovary, the theca cell tumor, has aroused considerable discussion, since there appears to be some doubt as to the actual existence of such a specific tumor type (Thomson and Sabler 1938; Novak and Brawner 1934). However, the pathologic picture, as well as considerations of embryologic development and other features suggest that the neoplasm is a distinct entity which deserves a place of its own in ovarian tumor classification.

Loeffler and Priesel (1932–33) were the first to describe a fibroma-like neoplasm producing estrogenic effects, as a 'fibroma thecacellulare xanthomatoides ovarii.' Since that time approximately 32 cases have been described, most of which were classified on purely morphologic criteria. Undoubtedly more cases will be discovered as pathologic material going back many years is re-examined. It is not unlikely that many of the cases reported in the literature as fibromas or fibrosarcomas associated with changes in sex characteristics fall into the theca cell tumor group. Their origin can be traced back to the unused or arrested cells of the primitive epithelial nucleus of the undifferentiated sex gland, differing from the granulosa cell tumor in that these cells would have made up the theca interna portions of the follicular apparatus if development had been complete.

The tumors vary in size from a small peach to that of an adult's head, and show surface lobulation (fig. 5). They may be cystic or solid, and are usually extremely hard to the touch. On section the cut surface presents a firm tissue closely resembling a fibroma (Fig. 6). The striking feature, however, is the presence of yellow areas which are irregularly distributed throughout the tumor and separated from each other by bundles of hyalinized connective tissue. Small or large cysts may be present, the result of degeneration. Micro-

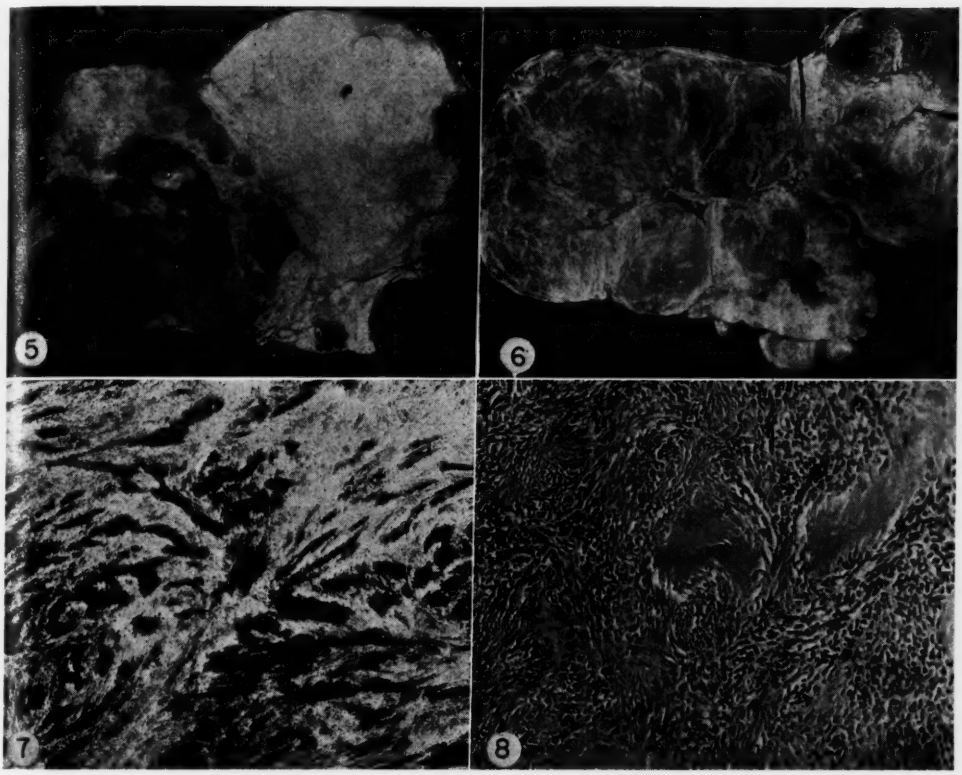


FIG. 5. Typical theca cell tumor with epithelial cell nests (dark areas) and hyaline connective tissue (light areas).
FIG. 6. Typical theca cell tumor with yellow lobules.
FIG. 7. Low power. Fat distribution in theca cell tumor (Sudan stain).
FIG. 8. Low power. Hyaline plaques and bundles in theca cell tumor.

scopically, the yellow areas are composed of plump spindle or polygonal cells usually showing centrally placed nuclei rich in chromatin. The cell cytoplasm is vacuolated and lipoid material in the form of double refractile bodies (cholesterol or cholesterol esters) has repeatedly been demonstrated. It is interesting to note that in contradistinction to the lipoid found in the granulosa cell tumor, that of the theca cell tumor is almost completely distributed within the cells themselves rather than in the extracellular connective tissue (fig. 7), while in the granulosa cell tumor the opposite distribution obtains. The connective tissue found outside the cellular areas is extensive, and hyalinized to a marked degree (fig. 8). Only 2 of the cases reported presented evidence of malignancy, *i.e.*, cellular islands composed or irregular cells with typical nuclei showing numerous mitoses and invasive growth.

Clinically, the tumor is unilateral and usually benign. It appears to develop most often in individuals who are past the menopausal age, one having occurred in a case at the age of 92, and only 4 cases in individuals within the child-bearing period. Since there have been no reports of the occurrence of the tumor in children one cannot describe the changes in secondary sex characteristics as being similar to those of the granulosa cell tumor. However, the presence of postmenopausal bleeding, the marked menometrorrhagia in young women, as well as the enlargement of the breasts at all ages is definite evidence of estrogenic activity on the part of the neoplasm, especially since removal is followed by an immediate remission of symptoms. The presence of an estrogenic

hormone has already been reported (Geist and Spielman 1935). The extract of the equivalent of 0.75 gm. of tumor tissue was found to contain 1 mouse unit of estrogen. This is more than can be demonstrated in an equivalent quantity of placental tissue and should leave no room for skepticism. Undoubtedly reports of the occurrence of the tumor in children will appear in the future which will further serve to prove its effects. The morphologic, the clinical, the chemical, and the hormonal characteristics are distinctive enough to allow for its classification as a definite entity. The importance of hormonal studies in the individual as well as of the tumor tissue is again stressed.

Treatment of the condition is exactly the same as that described in the discussion of the granulosa cell tumor, *i.e.*, conservatism in the young and hysterectomy with bilateral salpingo-oöphorectomy in the senium.

TUMORS PRODUCING MASCULINIZING EFFECTS

The tumors of the ovary which produce masculine effects in the individual are extremely interesting. The physical changes in the female harboring such a tumor are so profound that once observed they are never forgotten. However, it must be pointed out here that conditions other than ovarian neoplasms may also produce these changes, and that indiscriminate laparotomies for exploration of the ovaries in the presence of normal palpatory pelvic findings is to be condemned. Thorough investigations to determine the presence, especially, of adrenal cortical tumors or pituitary tumors (basophilic adenoma) in the absence of positive pelvic findings, as well as hormonal blood and urine studies, basal metabolism, blood counts, and vaginal smears, all should be performed before resorting to pelvic surgery. It is not unlikely that many needless operations are being performed in individuals showing some of the stigmata of masculinization, in the hope that a masculinizing tumor will be found. One repeatedly observes cases showing a greater or less degree of hirsutism accompanied by a pelvic tumor which on laparotomy turns out to be a pedunculated fibroid or a simple ovarian cyst which could not by any stretch of the imagination be associated with the virilism manifested by the patient. It must also be borne in mind that in spite of careful investigation by every means at our disposal no cause whatever may be found for the presence of virilism in many cases.

The tumors of the ovary which produce masculinizing effects and which are to be discussed in this paper are: arrhenoblastoma, adrenal rest tumor, 'luteoma,' (solid tumors with luteinization; lutein cell tumor).

Arrhenoblastoma. Although Pick (1905 b) was the first to describe the tumor which we now call the arrhenoblastoma, he believed that it arose from the male portion of a true ovotestis. It remained for Meyer (1930 a) however, properly to classify it by careful morphologic and genetic studies. The overwhelming majority of present day observers believe as he does, that the tumor arises from a male-directed element in the ovary, probably in the rete ovarii and medullary tubules described above, which represent the homologue of the tubuli seminiferi in the male, and which by their persistence give rise to the arrhenoblastoma. About 50 cases have been reported to date.

From the cases already described the variations in size of the tumor are not marked; it usually varies from that of a walnut to the size of a large orange. The surface of the neoplasm is smooth, lobulated, firm and encapsulated. Cystic areas may be present. On section it is seen to be firm in consistency, yellowish or gray in color, and scattered areas of hemorrhage and necrosis can be distinguished (fig. 9). There is a tendency towards lobulation, the lobules being well demarcated by the distribution of connective tissue. The yellow areas are also surrounded by connective tissue. Cysts if present are variable in size and contain a clear straw-colored fluid or a turbid, dark secretion depending upon the extent of necrosis.

Histologically, Meyer (1930 a) has divided the arrhenoblastoma into 3 types. These are the typical, the atypical, and the intermediate varieties.

The typical form is composed of single layers of low columnar or cuboidal cells which form typical tubular or adenomatous structures (fig. 10). The gland-like arrangement may

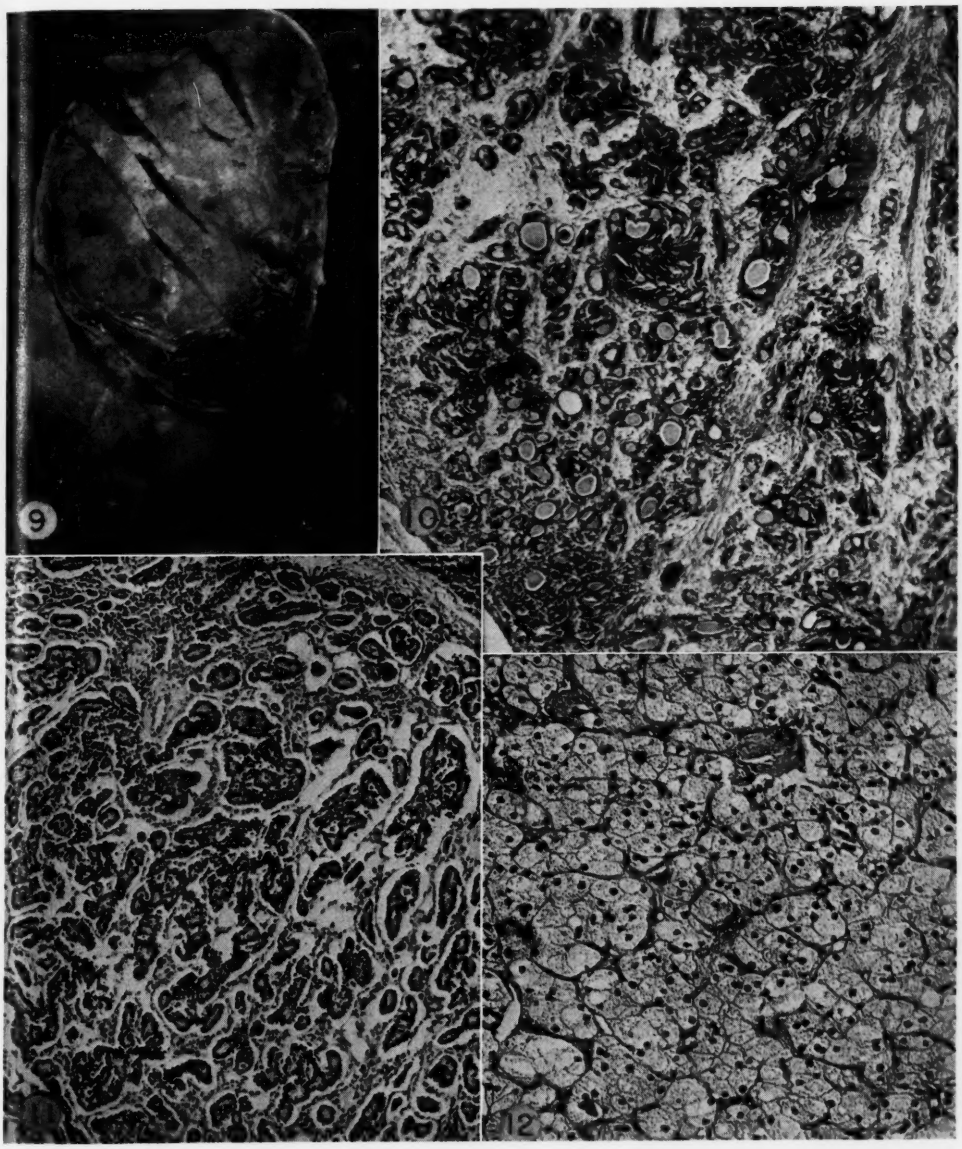


FIG. 9. Section of arrhenoblastoma with cavitation and hemorrhage.
FIG. 10. Low power. Intermediate type of arrhenoblastoma with atypical and typical structures. Note regularity of some of the tubules.
FIG. 11. Low power. A typical type of arrhenoblastoma with imperfect tubular arrangement. (Courtesy of Dr. R. Miller.)
FIG. 12. High power. Adrenal rest tumor. (Courtesy of Dr. Klein.)

resemble the interstitial cells of the testicle. The cells show a granular or vacuolated cytoplasm and the nuclei are round or irregular in shape. The tubules are surrounded by connective tissue which contains either a few spindle cells or many large pale granular cells resembling the so-called interstitial cells of Leydig. They contain lipoid which may be related to the production of hormones. Evidence of malignancy may be present as char-

acterized by mitoses, variations in cell structure, and irregular cell arrangement with a tendency toward invasion of the connective tissue.

The atypical form comprises groups of cells which appear in the main, as solid cords with only an occasional irregularly tortuous tubule (fig. 11). The latter may be convoluted so that no lumen is discernible. The cells are fairly large, oval in shape or spindle-shaped. There is a marked resemblance to sarcoma in some areas. Connective tissue is present between the cord-like structures but this is not as well preserved as in the typical form. There is a greater tendency towards vacuolization of the cells, fatty degeneration, hemorrhage, liquefaction and cyst formation.

The intermediate type presents combinations of the typical and atypical. Both well-formed glandular structures and irregular cell cords can be distinguished.

Although the tumor usually occurs in individuals between the ages of 16 and 50, cases have been reported in the postmenopausal period. The striking and characteristic feature of the arrhenoblastoma is the associated masculinization (or defeminization). In most of the cases reported the degree of masculinization seems to bear a distinct relationship to the degree of differentiation of the cells and their arrangement in the form of tubules, *i.e.*, the closer the approach to the typical form of arrhenoblastoma the fewer the signs of masculinization, and the greater the resemblance to the atypical form, the greater the degree of masculinization. The symptoms and signs consist of amenorrhea; hypertrichosis which is generalized and usually accompanied by a sufficient growth of the beard as to necessitate shaving; hypertension; a loss of the feminine skin texture and general feminine body contour; a deepening of the voice which changes to a baritone in quality; atrophy of the breasts; enlargement of the clitoris; and skeletal changes resulting in a resemblance to the male type. Sterility also occurs even though children may have been borne prior to the development of the tumor. Usually there is a loss of normal libido, accompanied by a variety of psychic disturbances which depend upon the physical changes primarily.

After the removal of the neoplasm the signs and symptoms usually regress almost completely. Changes in the bony structures and those of the larynx usually persist, however, so that the voice may remain deep in quality. Instances of pregnancy with the birth of normal children after the regression of symptoms have been reported.

The association of masculinization with arrhenoblastoma has been explained on the basis of production of large quantities of androgenic hormone on the part of the tumor. Up to this time, probably due to the paucity of material examined, this point has not been proved. As more cases are discovered and intensively studied, especially on a hormonal basis, this problem undoubtedly will be solved.

Treatment consists in extirpation of the growth. Although it is classified as being malignant, its potential of malignancy is not great, so that in young women both ovaries need not be removed. However, if the second ovary shows involvement or the patient is in or near the menopause both uterus and adnexa should be extirpated.

Adrenal rest tumor. That masculinization may occur in females showing cortical tumors of the adrenal gland is a well established fact. The recognition of the condition and removal of the involved gland has repeatedly resulted in a regression of symptoms. In the ovary this type of tumor may also be encountered and may also produce masculinizing effects. Genetically, it must be remembered that the primitive sex gland develops in close approximation to the mesonephros so that misplaced adrenal cells may come to rest in the region of the ovary as the latter descends into the pelvis. Such masses of lipoid-containing, large, vacuolated cells have been described as being present along the border of the infundibulo-pelvic ligament, within the broad ligament, in the region of the ovarian vessels and within the ovary itself. It seems more than likely that these cells may give rise to neoplasms. Our concern here, of course, is with the primary tumors of this type arising in the ovary. Those associated with tumors of the adrenal gland may be primary and independent in themselves or they may be metastatic. Since adrenal rest growths of the ovary may appear

long after (as much as 20 years) the removal of a primary adrenal neoplasm their origin from displaced cells seems logical.

The tumor varies in size from that of a walnut to a mass as large as a man's head. It is encapsulated, its surface is smooth and nodular, and on section its color is yellow or brown. It is soft and elastic in consistency. Connective tissue trabeculae are not conspicuous, usually due to a tendency toward hemorrhage and necrosis. Cystic areas may be present. Although the tumors may be confined to the ovary proper, in most instances they arise in the broad ligament and spread to the ovary. Microscopically, the growth is composed of large transparent vacuolated cells with definite cell membranes (fig. 12). The nuclei are small, stain darkly, and are centrally and eccentrically placed. The cells show a mosaic arrangement, are found mainly about the numerous fine vessels and, since there is little connective tissue, they lie directly on the capillary walls. They may form rows or tubules.

Clinically, the tumor is usually associated with virilism, although the degree may vary. All of the symptoms of masculinization described above may be present or only hypertrichosis and amenorrhea. However, regression of the symptoms upon removal of the neoplasm has repeatedly been seen. It must be emphasized that the adrenal rest tumor is highly malignant and its metastases may be widespread. Also, that the removal of such a tumor does not necessarily mean the eradication of all the cells capable of producing the growth. Small tumors elsewhere in the pelvis and not recognized may explain the continuation of symptoms even after operation. The fact that the adrenal gland may be involved must also be considered.

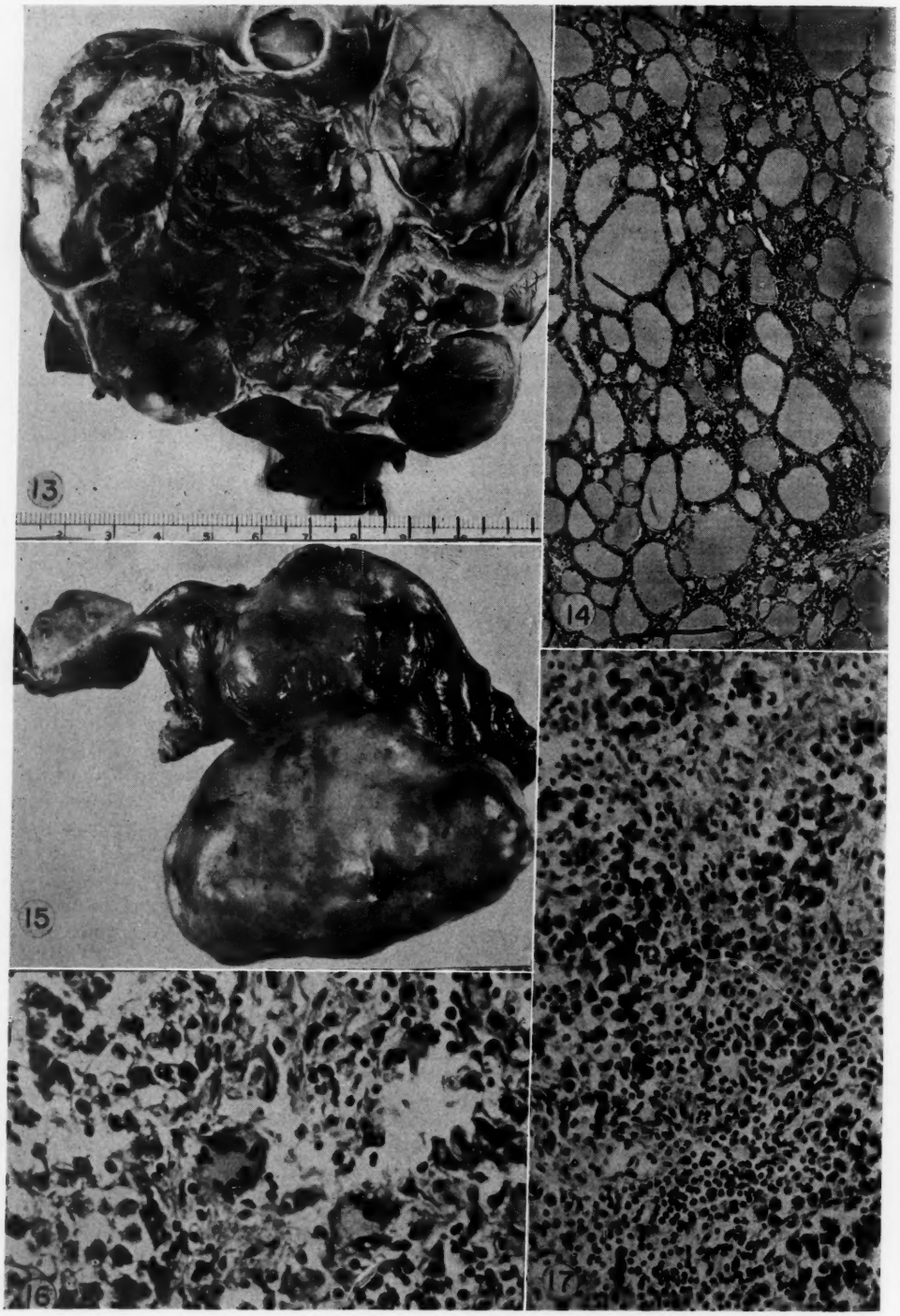
It is particularly interesting to note that in adrenal cortical tumors associated with marked masculinization, tremendous quantities of estrogenic hormone have been isolated both in the tumor tissue and in the blood and urine of the the patient. The significance of these findings is not at all clear. Studies to determine androgen formation in the individual and on the part of the tumor may help considerably.

The adrenal rest tumor at present is the cause of much speculation. It is being confused with luteinized tumors (usually granulosa or theca cell), with the so-called 'luteoma,' and even with atypical Krukenberg tumors. The luteoma is described below. The Krukenberg tumor has never been found to be associated with masculinizing changes, and is, of course, a metastatic tumor from the gastro-intestinal tract.

Treatment consists in operative removal of the neoplasm, if it is primary. Since it is highly malignant, in the young individual careful exploration of the entire pelvis even to splitting the second ovary, if in doubt, should be performed. When the ovarian growth is metastatic from a primary one in the adrenal gland, its removal is only indicated after the affected adrenal has been removed. Radio-therapy postoperatively has been recommended in malignant cases.

'Luteoma'; luteinized tumors; lutein cell tumor. As has been indicated above, the so-called luteoma is the source of controversy at the present time. Only 6 cases have been reported heretofore, and these have by no means proved acceptable as a distinct tumor entity. Because of the similarity of the pathologic picture of adrenal rest tumor, luteoma, and luteinization of other tumors of the ovary these 3 conditions must be carefully evaluated before any conclusion can be reached as to correct diagnosis. The confusion that exists is mainly due to the fact that morphologic studies show that there is little difference between even a mature corpus luteum and adrenal tissue undergoing proliferation within the ovary. Luteinized small granulosa and theca cell tumors may also produce a similar picture. However, differentiation is possible.

The luteoma, from such cases as have been described, appears to cause enlargement of the ovaries which may reach twice normal in size. Its color is yellow and consistency elastic. On section it presents a yellow, moist, glistening surface occasionally containing tiny cystic areas. White connective tissue strands radiate throughout the yellow tissue. Hemorrhage and necrosis are not common. The microscopic picture is exactly the same as that which characterizes the adrenal rest tumor. Lipoid can be demonstrated in the cells but glycogen is absent. The luteoma may also resemble a Krukenberg tumor.



FIGS. 13–17. See opposite page for legend.

Clinically, these tumors should produce a continuous secretory phase type of uterine endometrium. It is true that the premenstrual decidual reaction has repeatedly been described, but it must be emphasized that these changes may also be brought about by luteinized tumors. The masculinization which has also been reported (hypertrichosis, amenorrhea and voice changes), appears to us to be associated with the adrenal rest tumor. In other words, we believe that an ovarian neoplasm which presents the picture of a so-called luteoma, when accompanied by excessive bleeding, enlargement of breasts, and other feminizing influences, probably is a luteinized granulosa or theca cell tumor. On the other hand, when the neoplasm is accompanied by signs of masculinization it is to be regarded as an adrenal rest tumor. Since evidence of the actual existence of the luteoma is still lacking it would perhaps be better to await further investigations before accepting it as a true ovarian neoplasm.

Luteinization of theca interna cells has been observed in human ovaries and has artificially been produced in rats. Although evidences of masculinization accompanied these findings, the changes are attributable to hormonal effects produced by gonadotropic or adrenal hormones rather than to the luteinization itself.

Treatment, in view of the foregoing, consists in removal of tumor tissue. When bilateral enlargement of the ovaries is the result of hormonal stimulation, operation is not required.

Tumors Producing Effects Other Than Feminization or Masculinization

In this group 3 types of neoplasm are to be discussed and a fourth merely mentioned. They are: *a*), struma ovarii; *b*), dysgerminoma; *c*), chorionepithelioma of the ovary; and *d*), the Brenner tumor.

Struma ovarii. Struma ovarii is included in the discussion of endocrine tumors of the ovary because it also may produce hormonal effects. It bears no relationship to either feminization or masculinization. Its inclusion is based on the fact that it is a tumor composed mainly of thyroid tissue which not infrequently produces an excess of the thyroid hormone capable of reacting in the same way as enlargement of the thyroid gland itself.

Although the origin of the tumor may still be debated most observers are agreed that it arises as part of a teratoma in which all or most of the teratomatous elements have been replaced by thyroid tissue. Since small quantities of this tissue are frequently found in teratomas of the ovary, only those cases in which the thyroid element is the only tissue, or predominates in the neoplasm, are to classified as true struma. About 50 cases have been reported.

Pathologically, the tumor may appear as a tiny nodule or it may be as large as an adult's head (fig. 13). It is encapsulated and its surface is irregularly nodular. On section its color is that of the thyroid gland, waxy and brownish in appearance, and on cut surface it presents a honeycomb-like appearance, the varying-sized spaces being filled with tenacious, yellow-brown secretion. When seen under the microscope, the tissue is composed of alveoli lined by flat or cuboidal epithelial cells which have poorly defined boundaries and which contain small darkly-staining nuclei (fig. 14). In areas the structure may consist only of solid cords of cells in which lumina are absent. Occasionally papillary projections covered by high columnar epithelium are discernible suggesting the hyperplasia of the thyroid gland seen in true hyperthyroidism. There may also be evidence of invasive growth with perforation of the capsule, and this would represent malignancy. Connective tissue is usually scanty. The secretion in the alveoli stains homogeneously and gives the same microchemical reactions as the colloid material of normal thyroid tissue. In this connection many investigators have demonstrated iodine in quantities comparable to those found in the gland itself. Plaut 1933, by biologic tests on tadpoles as well as the Reid-Hunt reaction, identified the teratomatous struma as being true thyroid tissue.

FIG. 13. Struma ovarii. (Courtesy of Dr. Ludwig Emge.)
FIG. 14. Low power. Struma ovarii. (Courtesy of Dr. Ludwig Emge.)
FIG. 15. Dysgerminoma.
FIG. 16. High power. Giant cells in dysgerminoma.
FIG. 17. Medium power. Lymphocytic infiltration in dysgerminoma.

From the clinical point of view the most striking symptoms produced by the action of the tumor are those of hyperthyroidism. The loss of weight, tremors, tachycardia, nervousness and elevated basal metabolism correspond to the picture presented in primary involvement of the thyroid gland. The neoplasm may be benign or malignant, and when malignant is invariably accompanied by ascites. Intra-abdominal metastases may also occur.

Treatment consists in operative removal of the neoplasm. In malignant cases hysterectomy with removal of both adnexa should be performed.

Dysgerminoma. The dysgerminoma of the ovary is another interesting tumor whose genesis and effect upon the individual is not entirely clear. It is discussed in this paper because reports of its association with one of the hormones (the gonadotropic) have appeared, and because in the general classification of ovarian neoplasms it is related to such tumors as the granulosa cell, theca cell, and arrhenoblastoma (Geist 1942).

As has been described the granulosa and theca cell tumors have their origin in a cell which may be said to be of the feminine type (the granulosa and theca cell), and the arrhenoblastoma in a male-directed cell type. The dysgerminoma, in the opinion of present-day investigators, probably originates from a neuter cell which goes back to the early epithelial nucleus, and which is neither masculine nor feminine from its inception. Absolute proof of this theory is lacking but certain facts seem to support the concept. These include the frequent occurrence of the tumor in underdeveloped or otherwise defective gonads in both males and females, or even in the ovotestis of hermaphrodites. It is also seen in such combinations as an aplastic gonad on one side and a tumor (dysgerminoma) on the other, and ovotestis on one side and tumor on the other. In the male it is called 'seminoma,' and it is also known as large round cell sarcoma.

The neoplasm is rounded, nodular, solid, and surrounded by a thin capsule which may be perforated by the tumor tissue. It may reach the size of an adult's head (fig. 15). On section it is yellowish gray in color, soft and elastic in consistency, and shows a tendency toward hemorrhage and necrosis. Cysts are usually present which are the result of degeneration and which vary in size up to that of an orange. The tissue is extremely friable and is easily torn on manipulation. The capsule may be perforated by the tumor so as to form adhesions and metastases to surrounding organs. Microscopically, it is found to be composed of large, round or polygonal uniform cells containing granular pale-staining cytoplasm and central nuclei which stain darkly. The arrangement of the cells may be in the form of strands, rows, or alveoli, and these are separated from each other by fine connective tissue septa. Giant cells are not infrequently seen often surrounded by fibroblasts resembling granulation tissue (fig. 16). Connective tissue is rather scanty, and it may be hyalinized. One of the striking characteristics of the morphology of the tumor is the lymphocytic infiltration of the connective tissue (fig. 17). Ovarian tissue may be present and show an entirely normal picture with follicles, corpora lutea and stroma.

Clinically, the tumor is usually unilateral, but bilateral occurrence is not uncommon. It is found most often in young women either just before or after the onset of puberty, and especially in the hypoplastic, asthenic type. Older normal women, however, may also harbor the neoplasm. The menstrual cycle is usually affected by the presence of the tumor, amenorrhea being the rule. Due to the aplasia or hypoplasia present, there may be no history of the establishment of menstruation. On the other hand, the females may have been entirely normal and may even have borne children. Very few cases have shown menorrhagia or metrorrhagia. Not infrequently one also finds a small atrophic uterus, infantile external genitalia and an enlarged clitoris. Hypertrichosis has rarely been observed. The tumor is highly malignant, metastases and recurrences following operation being common.

It is interesting to note that such hormonal studies as have been performed in individuals manifesting this type of neoplasm, have invariably shown the isolation of a gonadotropic hormone. Thus, Spielman and Morton (1938), Fauvet (1936), and Bluemel (1934) have demonstrated this hormone in the urine or tumor tissue, of both males and females. The reaction

in some of the cases has been strong enough as to produce luteinization of the immature animal ovary, while the estrogen reaction was negative. Although these findings cannot be explained at the present time, the similarity to the hormonal conditions which exist at the menopause (increase in gonadotropic, decrease in estrogenic hormones) is suggested. However, additional studies must be made on many more cases before any conclusions are warranted.

The treatment is operative. In older women radical removal of uterus and adnexa is indicated, and in the young, extirpation of all tumor tissue. It is particularly stressed that the second ovary must be carefully investigated for involvement. In one of the cases observed (Spielman and Morton 1938) although one ovary was the site of a large tumor, the other ovary contained only a small nodule about 1 cm. in diameter which could easily have been overlooked. When both ovaries are removed, postoperative radiotherapy should be utilized.

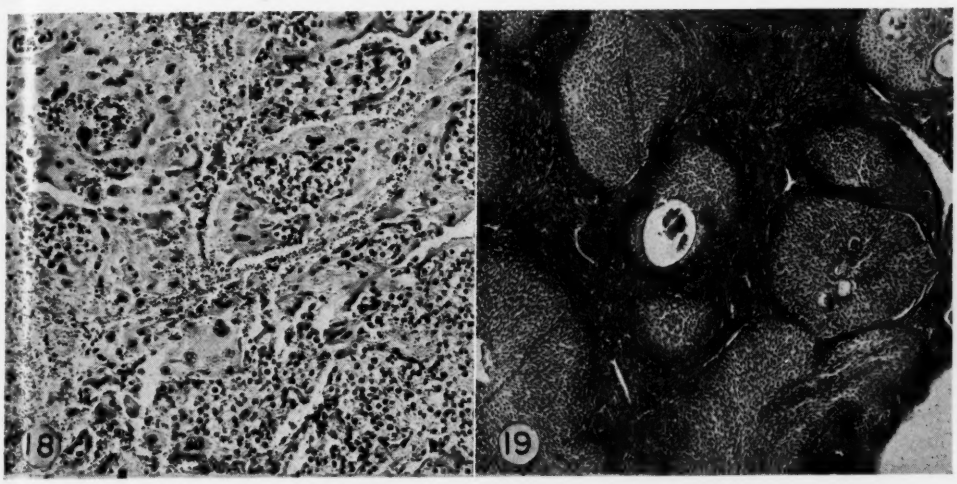


FIG. 18. Low power. Chorionepithelioma of ovary.
FIG. 19. Medium power. Cell nests composing Brenner tumor with tubules, beginning cyst formation, and pseudomucinous-like epithelium (lower right).

Chorionepithelioma. Chorionepithelioma of the ovary is a very rare tumor, and its recognition is usually not easy. Although cases of so-called 'primary' chorionepithelioma have been described, these probably represent either sarcoma or carcinoma in which there is an atypical cell arrangement closely resembling syncytium. Actually, in the authors' opinion, true chorionepithelioma is either secondary or metastatic. It is secondary when it arises following a primary ovarian pregnancy or from the endodermal components of a teratoma, and metastatic when it is the result of metastases from a primary chorionepithelioma elsewhere. It is a true endocrine tumor since it produces tremendous quantities of one of the important hormones, *i.e.* the gonadotropic.

The neoplasm may be very small or may be as large as an adult's head. Its surface is nodular and hemorrhagic, and it is usually surrounded by a thin friable capsule. On section it is seen to be reddish-purple in color due to the blood present, and such tissue as can be distinguished resembles placental tissue. The tumor is traversed by firm white translucent bundles and plaques. Microscopically, sections show masses of small, dark-staining nuclei arranged in plaques or rows within an amorphous matrix-like tissue. Cell boundaries are indistinct or may be totally absent, so that the neoplastic tissue appears as large masses of cytoplasm containing numerous nuclei, or large groups of nuclei in relatively little cytoplasm (fig. 18). Associated with this syncytial tissue there may also be collections of relatively large polyhedral cells with distinct cell bodies, granular or vacuolated cytoplasm, and central well-defined

nuclei rich in chromatin. These represent the typical Langhans cells which with syncytium characterize chorionepithelioma. When the tumor has its origin in a teratoma, other types of tissue such as undifferentiated glands, neuroepithelium and cartilage may also be found.

Chorionepithelioma of teratomatous origin is usually found in children and is not infrequently associated with the symptoms of premature puberty already enumerated. The changes in secondary sex characteristics in these cases is due, of course, to the elaboration of the gonadotropic and the estrogenic hormones which act upon the breasts, uterus and vagina to bring about a premature sexual maturity. Neoplasms originating either in primary ovarian pregnancy or from chorionepithelioma elsewhere (metastases) may produce such effects as abnormal uterine bleeding even to the point of severe anemia, enlargement of the breasts, and hyperemia of the vulva and vagina. Regardless of origin it must be recognized that chorionepithelioma is an extremely malignant tumor often accompanied by ascites, pain and weakness, and showing a marked tendency toward early metastases especially to the lungs, the brain and the liver.

As can be seen, hormonal assays of blood and urine will readily differentiate this type of neoplasm from any of the others, since only in hydatid mole or chorionepithelioma of the uterus can such high titers of gonadotropic hormone be demonstrated. An increase in the estrogenic hormone titer is also to be expected.

Although the prognosis is poor, attempts at the radical removal of all neoplastic tissue is always justifiable. Radiotherapy alone has been advocated by some observers due to the danger of dissemination of tumor tissue. In the authors' opinion, operation followed by radiotherapy are the procedures of choice.

Brenner tumor. For the sake of completeness this tumor may be mentioned since it falls in the group which has been designated as primary parenchymatous epithelial neoplasms of subsurface origin (Geist 1942).

The Brenner tumor is related to the other tumors in that it also arises from primitive epithelial cells which appear in the form of nests especially in the rete ovarii. They have been designated as Walthard's cells and are probably a type of indifferent epithelial cells analogous to the type which produces the dysgerminoma. Its frequent association with other ovarian neoplasms (pseudomucinous and papillary serous cysts and fibroadenomatous tumors) suggests a derangement of growth of the primitive ovary.

The tumors are solid or cystic, variable in size, nodular, and are composed of branching strands of indifferent large cells containing glycogen. The arrangement is typical, the collections of cells being sharply demarcated from the dense collaginous connective tissue stroma in which they lie. Degeneration with liquefaction within the cell nests is common (fig. 19).

The Brenner tumor, although exceedingly interesting from a morphologic and genetic point of view, produces little effect upon the individual. There are no special symptoms other than those of the presence of a tumor. Usually it is discovered by accident. Menstruation is not affected nor does it produce any known endocrine change in the host.

It is entirely benign and although operative removal is indicated, conservatism should be practiced.

CONCLUSION

An attempt has been made to describe the neoplasms of the ovary which are associated with endocrine effects. That which is presented above represents a resumé of our knowledge to the present time. As has been stressed so frequently throughout this paper, considerable work remains to be done in order to clarify the subject. That certain tumors of the ovary can produce profound changes in the female as a whole has been definitely established. The *modus operandi* in all cases, however, is still far from clear. The advances that have been made in the field of endocrinology as it applies to the female have been gratifying but many questions remain unanswered. It is again suggested that hormonal studies of the individual harboring an ovarian neoplasm, both before and after removal, as well as on the tumor tissue itself, offer the greatest hope for enlightenment in the future.

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Psychology of the Menstrual Cycle

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IN MANY primitive cultures menstruation has been ascribed to the cycles of the moon or tides. It has, moreover, been thought of as a dangerous condition requiring various taboos. Frazer in his 'Golden Bough' cites countless restrictions imposed upon the menstruating woman for the protection both of herself and the community. Even today there are cautions observed during the menstrual period which are directly descended from these earlier superstitions. The prohibition of bathing—originally intended to protect the local stream, used in common by the whole tribe, from contamination by menstrual blood—is a good example of such survival. In this sphere as elsewhere, however, knowledge gradually replaces superstition and physiology and psychology elbow out lunar myths and tribal taboos.

It is now well known that sex hormones follow a definite pattern in the menstrual cycle. While estrogen gradually increases with the ripening of the follicle and sharply drops off after the ovum is released, progesterone begins its upward course just prior to or at about the time of follicle rupture. In the event that pregnancy does not occur, the amount of the latter hormone likewise decreases about a week after its initial production. At the time of ovulation both hormones are, in the ordinary case, present to some extent. They are both at a minimum in the late pre-menstrual period.

Certain related facts of physiology are of interest. Among these are changes in basal metabolism and body temperature. Since the classic work of van de Velde (12) in 1905 it has been known that certain changes in temperature accompany the menstrual cycle. The body temperature is ordinarily at its lowest coincident with ovulation, when estrogen is maximum. As progesterone is produced the temperature gradually rises to a peak which roughly coincides with the maximum production of that hormone. The temperature then drops as progesterone decreases and continues downward as estrogen gradually increases. The question may accordingly be raised as to whether the term 'heat' as applied to estrus in the lower animals may not also have its application to woman. Animals are maximally receptive to their mates during the period of 'heat' associated with ovulation. The human female seems not to be very different in this respect.

Present knowledge of the menstrual cycle distinguishes clearly between ovulation and menstruation. Until quite recently this distinction was not understood. The error resulted from the fact that estrus, or sexual receptivity, and accompanying ovulation in the lower animals is often characterized by a vaginal discharge readily confused with the menstrual flow of women.

The differentiation of ovulation and menstruation in a sense renders the term *menstrual cycle* a misnomer. Menstruation being a negative phase that occurs by default, the more appropriate designation would be *female sexual cycle*. The implication of this term is—rightly—that the 'aim of nature' is a positive one, menstruation taking place only when this aim is thwarted. This qualification being noted for subsequent elaboration, the more usual term *menstrual cycle* may for the present be kept. For the phases of the cycle, however, the terms pre-ovulative and post-ovulative, on the one hand, and pre-menstrual and menstrual, on the other, are used here throughout in order to emphasize appropriately the positive and negative aspects of the complete chain of events.

Fragmentary clinical information about the psychologic aspects of menstruation has long been available. Chadwick (5, 6) well summar-

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izes this knowledge. But for a systematic approach to the entire menstrual cycle the study made by Benedek and Rubenstein (3, 4) is outstandingly significant. Benedek, a psychoanalyst in Chicago, had under observation several neurotic women who regularly brought her their dreams and discussed their problems. Her psychiatric colleagues supplied corresponding records for some of their patients. In this way the most intimate psychologic material accompanying 75 menstrual cycles in 15 patients became available. Rubenstein, a physiologist in Cleveland specializing in the endocrine aspects of the sexual cycle in women, independently studied a continuous series of vaginal smears made by the patients in question (after instruction by a woman physician) and of rectal temperatures taken simultaneously. On the basis of the psychologic observations Benedek completed presumptive calendars of the menstrual cycles. From the vaginal smears and body temperatures Rubenstein made similar predictions. When the two sets of tables were compared a high amount of agreement was found. A method for investigating the psychosomatics of ovarian function was thus established and revealed certain striking interrelationships.

The pre-ovulative phase of the cycle, with its rising tide of estrogen, is psychologically marked by strong heterosexual drives either overt or disguised. During this period the patients studied were found to be distinctly oriented toward men. Destructive trends—desires to injure or kill, as reflected, for example, in dreams—were noted, but the prevailing feature was an outgoing orientation toward individuals of the opposite sex. With sexual gratification, the high tension of this period was relieved; otherwise tension mounted.

With the rupture of the follicle a relaxation of tension supervened, to be followed, as progesterone increased, by a passive receptive trend. A desire to be loved and possessed now came to the fore. Sometimes a conflict between the active heterosexual tendencies of the estrogenic phase and the more passive attitude of the early progesterone stage was observed. As estrogen sharply diminished and progesterone rapidly increased, a concentration of interest on the woman's own body became dominant. Her dreams and fantasies reflected a desire to be nurtured and an attitude of self-nurture. With failure of fertilization and the decrease of progesterone, the passive-receptive attitude continued but pregnancy fantasies became prominent. A recurrence of heterosexual tension associated with the reappearance of estrogen was also occasionally found.

It is thus clear that the changes in sex hormone production are correlated with certain changes in psychologic orientation. Both together appear to have a bearing upon the biologic reaction of the organism at the periods in question. In the pre-ovulative phase of the cycle, when estrogen is increasing and the ovum is maturing, the chief business of the female would naturally be the acquisition of a mate. In the normal course of events this phase would presumably be over with the coming of ovulation. With the production of progesterone the uterus is prepared for the reception of the fertilized ovum and a more passive attitude would supervene. As the pregnancy preparation gradually increases during the post-ovulative phase the orientation might well become more and more a matter of nurturing. The ovum which is to be or has already been fertilized in the fallopian tube should soon be descending to the uterus where it will be implanted in the walls to grow and develop into a child. Consciously or unconsciously the woman would therefore at this phase be preoccupied with her own body—the nest of her offspring.

The pre-menstrual and menstrual phases which now supervene represent, as already noted, a negative adjustment that will not occur if fertilization has led to pregnancy. A minimal secretion of sex hormones is apparently the stimulus for the expulsion of the tissues, which, in the absence of fertilization, become waste. Psychologically the attitudes of the woman during this time are again adaptively characteristic. Pregnancy fantasies are not uncommon but regressive infantile sexual attitudes are also observed. 'Eliminative' psychologic trends become pronounced as seen, for example, in preoccupations about vomiting, oral or urethral discharge, abortion and bleeding. Emotional depression is prominent, especially in the transitional days, but the flow itself often brings a relaxation of tension.

Certain cautions are indicated. It must, for one thing, be noted that the attitudes depicted are by no means inevitable. They represent implicit rather than explicit orientations, not so much overt as potentially ready to seek expression at the first opportunity. The fluctuations above reported would hence seldom be recognized by the woman herself or most unprepared observers. This conclusion is strengthened by the fact that cyclic changes even when overt are of gradual occurrence and not easily detected. Furthermore, as in so many cases of unconscious attitudes, the environment usually offers sufficient 'excuse' to explain the mood or feeling of the moment; and the attitude itself, though perhaps basically prepared on other grounds or merely accentuated by the environmental occasion, is assigned completely to the latter. Not that these occasions are entirely negligible; they are in part fairly important in bringing out the prepared pattern of response. The more adverse the environmental conditions, the more extreme the reactions will be, in the determined direction. Again, it must be observed that these directions of response do not become crystallized with equal readiness in all women. Psychologically mature and well-adjusted women may resist them quite adequately and exhibit comparatively little fluctuation throughout the cycle. Such alterations would, on the other hand, be naturally exaggerated in neurotic individuals. The clarity of Benedek and Rubenstein's observations may perhaps be attributed to the fact that not only were their subjects neurotic but that the psychoanalytic method focusses on just those implicit attitudes which would otherwise escape attention.

The very recent study of Altmann, Knowles and Bull (1) confirms the picture above sketched. They found that before the onset of menstruation an outburst of physical and mental activity is characteristic and is paralleled by a corresponding peak during the ovulative phase of the cycle. The activity of the premenstrual phase was, however, associated with tenseness and irritability, sometimes depression, while that of the ovulative phase showed freedom from mental discomfort and generally bore the marks of elation.

The outstanding difference to be noted is thus the rather positive or progressive orientation in the ovulative part of the cycle as contrasted with the negative and regressive orientation characteristic of the menstrual segment. The difference appears not only in the physiologic production of sex hormones but equally in the psychologic attitudes of the woman.

The menstrual phases deserve further psychologic comment since considerably more is known about them than about the ovulative phases. The most general and outstanding reaction to the menstrual period is depression. Chadwick (5) has given an excellent summary of the mental status of this phase of the sexual cycle. Tearfulness and anxiety, suspicion and tendencies towards self-pity or self-reproach are common features, in addition to a general feeling of low spirits and some irritability. Frightening dreams sometimes occur. Forgetfulness, obsessions, especially as regards cleanliness, and occasionally fantasies of pregnancy prevail. Supplementing these clinical observations are some statistical studies that may be cited. From the findings obtained by means of a questionnaire McCance, Luff and Widdowson (10) have discovered that mental depression is at a maximum two days before a period, diminishes until the eleventh day, increases slightly up to the seventeenth, diminishes to the twentieth, and finally increases. By a similar technique Conklin, Byrom and Knipes (7) found that the characteristic orientation during the menstrual period is introversive, *i.e.*, one in which the subject turns in upon herself instead of engaging in outward-going activities. Perhaps the most interesting investigation along the present lines is that of Balazs (2). From a study of 3110 cases of suicidal attempt he discovered a trend which may be summarized in the following index figures: menstrual: 4.7; post-menstrual: 4.2; intra-menstrual: 3.3; pre-menstrual: 2.8. Balazs indicates that his results contradict those of previous investigators, *e.g.*, Krafft-Ebing, who regarded the pre-menstrual period as the most hazardous from the standpoint of suicidal attempts. However, his data are easily reconciled with the rest if one notes that while a maximum of depression may occur in the late pre-menstrual

phase, suicidal attempts may most commonly be precipitated on the first day of menstruation as an end result.

The state of affairs in the organism at the menstrual period is more complex than during earlier phases of the cycle. While ovarian deficiency can not be overlooked in attempting to explain the feelings of low energy and irritability of which women complain at this time, the hormones alone are insufficient to account for all that happens. According to Hoskins (8), 'Menstruation . . . marks a frustration of nature—the acknowledgement of failure of fertilization.' This total biologic context must be carefully considered if justice is to be done to the various features of the woman's reaction. Metchnikoff (11) long ago pointed out that menstruation is in a sense abnormal. It would not occur if pregnancy had taken place as nature 'intended.'

The first and most obvious aspect of the frustration which the menstrual flow implies concerns the fate of the ovum itself. Although prepared for fertilization, the ovum has not been fertilized. The hormones keep pace with this negative outcome. Progesterone decreases markedly while estrogen is also waning. The menstrual flow is apparently set off by the regression of the hormones as a stimulus.

A second aspect of the reaction to frustration which is involved concerns the appearance of blood. To the primitive mind, and even to many civilized individuals, blood is naively taken as a proof of guilt and death. Thus, to a girl who has not been prepared for menarche the sight of the first menstrual blood may evoke fear and shame. The 'affliction' may even be regarded as punishment for secret sins like masturbation. Such an attitude on the part of the woman is complicated further by the social taboos which, as already mentioned, have from earliest times surrounded menstruation. It has, for instance, been believed that if a menstruating woman walks through a field of wheat the crop will be ruined. Similarly, it is thought even today by some individuals that flowers will wither if worn during menstruation. In many primitive tribes women have accordingly been segregated as an initiatory rite at puberty and regularly thereafter during the monthly periods as a protective measure. The effect of such treatment on the woman herself is not difficult to imagine. The inferiority and guilt feelings which the flowing of the blood alone suggests is strongly enhanced. These effects of social conditioning when added to the psychologic correlates of the abortive endocrine process not unnaturally make for the depression and irritability observed in women just before and during the menstrual period.

The above is obviously a paradigmatic schema only. A particular woman will never do more than approximate it. But on the evidence now available the picture holds for the typical case if carefully observed. The extent to which it may be modified by individual differences in endowment and experience is nevertheless very great. Thus certain attitudes toward menstruation may be taken over by the young girl through imitation or identification. It has often been observed clinically that whether or not a girl is unduly disturbed or fatigued or whether she goes through the menstrual period quite normally is correlated with similar attitudes on the part of the older women in her environment. Of similar interest are the more transient effects of current emotion on menstruation.

No account of the psychologic factors involved in the menstrual cycle would be complete without some recognition of the part which the climacteric plays as related to earlier menstrual symptoms. Something in the nature of an analogy is here in order. Just as the early adolescent period, when menstruation has just begun, may be thought of as corresponding to the active heterosexual stage which is found in the pre-ovulative period of the menstrual cycle, so, proceeding with the analogy, the adjustment of the mature maternal woman corresponds to the more passive and receptive orientation of the ovulative and post-ovulative stages. Finally, the menstrual period itself would be paralleled, as a frustration of nature, by that frustration on a grander scale which is ushered in by the menopause. Whereas the menstrual period represents a failure of fertilization in an individual cycle, the menopause represents the failure of the whole life cycle in respect to procreation. Any symptoms which

might have been present as a reaction to frustration microcosmically during earlier menstrual periods might thus very naturally be found in exacerbated form on the macrocosmic level of the menopause. The common occurrence of involutional psychoses in women can hence be appreciated. From a similar standpoint to that here adopted in interpreting the menstrual phase of the monthly cycle, Malamud, *et al.*, (9) in a recent discussion of involutional psychosis have maintained that the withdrawal of hormones is but one aspect of a more general psychobiologic frustration.

SUMMARY

If one examines the female sexual cycle as a whole, the following condensed picture thus seems to emerge on the basis of what is at present known about physiologic and psychologic interrelationships. In the pre-ovulative phase, when estrogen is being produced in increasing amounts, an active heterosexual trend is predominant. The post-ovulative phase, in which progesterone is secreted, is accompanied by a shift of attitude. Interest is now more apt to be centered in the woman's own body. Both phases seem psychologically to have a forward-looking character. The pre-menstrual phase, which already signalizes the failure of fertilization, radically alters the picture. While on the physiologic side sex hormones are now at their lowest titre, on the psychologic side, 'eliminative' and 'cleansing' trends appear. Attitudes of inferiority and guilt may be present. As a compensation, fantasies of pregnancy may occur. With the actual onset of menstruation and during the flow, a sense of depression, sometimes expressed as irritability, is not uncommon. This type of response becomes intelligible if the menstrual flow is regarded as the result of a biologic frustration to which the woman is reacting psychologically as well. But as estrogen begins once more to increase with the beginning of a new cycle, a more positive orientation supervenes. All in all there could hardly be a more dramatically revealing demonstration of the unity of psyche and soma. As a problem in psychosomatic medicine the relationships here in question are rich in possibilities for future research.

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COMMUNICATION

THE URINARY KETOSTEROIDS—REPORT OF CONFERENCE[1]

WITH THE DEVELOPMENT of microchemical methods for the extraction and determination of urinary steroids, numerous attempts have been made to determine the physiologic and clinical significance of the excretory levels, particularly of the 17-ketosteroids. Much difficulty has been encountered in comparing data from different laboratories due to variations in the methods of extraction and determination employed. In an attempt to secure some agreement on essential technical methods and to initiate discussion of general interpretations and results, the Josiah Macy Jr. Foundation called together for a conference on June 7, 1942 a group of active investigators in the field under the chairmanship of Dr. Elmer Sevringhaus.[2] A summary of the findings of this conference is presented here in the hope that endocrinologists generally may be benefited. A large body of useful data and opinion was made available by the individual conference members. In presenting this abstract of it the writer wishes at once to absolve the individual conference members from responsibility for any sins of interpretation that may be his doing.

The principal 17-ketosteroids that have been isolated from human urine and identified chemically are androsterone and two of its isomers, isoandrosterone and etiocholanol-3α-17-one; dehydroisoandrosterone; androstenone-17; $\Delta^{3,5}$ androstadieneone; and estrone. Estrone is an estrogenic phenolic steroid that is usually separated by extractive processes from the other 17-ketosteroids listed. These latter are all considered androstane derivatives (having 19 carbon atoms in the typical steroid skeleton) and have been loosely called the urinary 'androgens.'

In urines of normal men and women, androsterone and etiocholanol-3α-17-one are the principal 17-ketosteroids and are sometimes called the α-17-ketosteroids; they cannot be precipitated from solution by digitonin. Isoandrosterone and dehydroisoandrosterone are the urinary β-17-ketosteroids; they are digitonin-precipitable and are present in normal urines in smaller amounts. Androstenone-17 and $\Delta^{3,5}$ androstadieneone are non-alcoholic 17-ketosteroids, and only the former has hitherto been isolated quantitatively (but in small amount) from normal urine.

The α and β-ketosteroids are not excreted into the urine to any extent as free compounds, but as esters. The recent work of Venning and of Gallagher indicates that these are sulfuric acid esters. The chemical extraction of these sulfates is a laborious and difficult procedure. An hydrolysis of the urines containing them is therefore practiced, since the free steroids are easily extractable with organic solvents. Strong mineral acids, such as HCl or H_2SO_4 are added to fresh urines and the practice is to heat (with or without refluxing) to boiling for a short period of time. The procedures using HCl are as follows: *a*) boiling for 7 to 10 minutes with 10 to 15 per cent HCl by volume added to the urine; *b*) refluxing for one hour after addition of 4 per cent HCl by volume. Alternatively, H_2SO_4 is added to 5 per cent by volume to urine and boiled for 15 to 30 minutes. There is some reason to believe that the non-alcoholic 17-ketosteroids may arise as a result of the hydrolytic procedure (*e.g.*, androstenone-17 from androsterone and its isomers $\Delta^{3,5}$ androstadienone from dehydroisoandrosterone).

The organic solvents employed for extracting the 17-ketosteroid from urines are those immiscible with H_2O; the principal ones now in use are ethyl ether, benzene, toluol and carbon tetrachloride. These extractives may be employed after the hydrolized urines have been rapidly

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[1] The permission of the Josiah Macy, Jr., Foundation, extended through Dr. Frank Fremont-Smith, for publication of the data has been gratefully received.

[2] Those attending were Drs. Sevringhaus, Harold Wooster, Carl Bachman, Maximilian Ehrenstein, W. K. Cuyler, Emil J. Baumann, K. Dobriner, Frank Fremont-Smith, Seymour Lieberman, C. P. Rhoads, Ephraim Shorr, J. Black, Ralph Dorfman, Gerald Evans, Leo Samuels, Patricia Smith, Harry Friedgood, Louis Fieser, E. Reifenstein, Jr., Nathan Talbot, Ira T. Nathanson, Gregory Pincus, John K. Wolfe, T. F. Gallagher, William T. Salter, H. R. Catchpole, J. S. L. Browne, Eleanor Venning, Hans Selye, P. Selye, and Captain F. A. Wickersham.

cooled or may be circulated in an extraction apparatus during the urine hydrolysis. When simultaneous hydrolysis and extraction are employed, benzene, toluol and carbon tetrachloride are the usual extractives, and the solvent is circulated from 3 to 4 hours. When it is desired to extract urinary estrogens as well as the 17-ketosteroids, carbon tetrachloride should be avoided as it is a poor solvent of estrogen. Ethyl ether appears to be the best general steroid extractive, but it should be free of organic peroxides, and because of its explosive qualities should not be used in a mechanical extractor.

The lipid material extracted from acid-hydrolized urines contains organic acids, various pigments, the neutral urinary steroids and phenolic substances. A number of non-steroidal substances, including acids and certain pigments, may be removed by washing the organic solvent with $NaHCO_3$ and Na_2CO_3. The phenols (including the urinary estrogens) may then be removed by strong alkali (1N to 5N NaOH is usually used). The organic solvent remaining (washed free of alkali with H_2O) contains neutral lipids, including the neutral 17-ketosteroids. This 'crude neutral' fraction is the one employed either for androgen or total 17-ketosteroid assay or for further extraction. The crude neutral fraction should not be kept in solution if it is to be held for later assay, but should be kept dry after evaporating off the solvent.

The crude neutral fraction may be assayed for total androgenic activity by administration to test animals. The assay result obtained will depend largely on the nature of the androgenic steroids present. The I.U. of androsterone is 0.10 mg. In the assay using the baby chick, for example, 0.10 mg. of isoandrosterone is equivalent to 0.12 I.U. of androsterone; etiocholanolone, to 0.00 I.U. (*i.e.*, inactive); dehydroisoandrosterone, to 0.33 I.U.; androstenone, to 0.08 I.U. (Dorfman).

For quantitative determination of 17-ketosteroids, various modifications of the colorimetric reaction of m-dinitrobenzene with ketones in alkaline solution have been employed. This reaction, originally described by Zimmerman, involves the development of a pink color (having an absorption maximum at 520 $\mu\mu$) by the 17-ketosteroid. When the reaction is applied to the crude neutral fraction of urine, the typical pink color is in part obscured by other colors that develop simultaneously. The presence of the atypical colors leads to an over-estimate of the 17-ketosteroids present. To obviate this over-estimate, certain color correction equations have been suggested (Fraser, *et al.*, *J. Clinical Endocrinology* 1: 234. 1941; Talbot, *et al.*, *J. Biol. Chem.* 143: 211. 1942) which, on certain assumptions, purport to correct for the chromogen which is not 17-ketosteroid. Since much of the atypical chromogen is non-ketonic, micro-methods have been devised which make possible the separation of the ketones of the crude neutral extract from the non-ketonic material (Talbot, *et al.*, *J. Biol. Chem.* 136: 365. 1940; Pincus and Pearlman, *Endocrinology* 29: 413. 1941). The Zimmerman reaction is then applied to the neutral ketonic fraction. Methods for removing interfering chromogen by adsorption have been suggested by several investigators (*e.g.*, Baumann and Metzger *Endocrinology* 27: 664. 1940), but the possibility of non-specific adsorption must be avoided.

The two current modifications of the Zimmerman reaction differ in that one involves the development of color in an aqueous alcoholic solution of the reagents, whereas in the other absolute alcohol is used as the solvent. According to Nathanson (in press) the two methods can be brought into good agreement if sufficient time for color development be allowed in each. Thus in the absolute alcohol method, urinary extracts (at 25°C.) develop full color in 80 minutes, whereas in the Holtorf-Koch aqueous alcohol method 105 minutes are requisite (*J. Biol. Chem.* 135: 377. 1940).

Two other methods for the determination of urinary 17-ketosteroids are available. Of these one is colorimetric and involves the development of a blue color by the application of $SbCl_3$ to the neutral ketonic extracts of urine (Pincus, *Endocrinology* 32: 176. 1943). It appears to be more specific than the Zimmerman reaction, but dehydroisoandrosterone is only feebly reactive. Also more specific is the polarographic method (Wolfe, *et al.*, *J. Biol. Chem.* 136: 653. 1940) which also requires the application of a ketone reaction. The polarographic method requires expert handling of delicate physical apparatus. If ketosteroids other than the 17-ketosteroids (*e.g.*, 3-ketosteroids or 20-ketosteroids) are present in urine extracts, they will contribute to the Zimmerman titer in both crude neutral and ketonic neutral fractions, especially in pregnancy urines which contain large amounts of 20-ketosteroids (epipregnanolone, epi-allopregnanolone, allopregnanolone). The $SbCl_3$ reaction largely excludes such compounds, but the 20-ketosteroids may complicate the polarographic method.

The identification of specific urinary ketosteroids requires the application of methods of chemical isolation and can be conducted only

with large quantities of urine. For routine work the separation of various groups of substances may be affected. Thus the β-ketosteroids can be separated from the α-ketosteroids by digitonin precipitation (Talbot, *et al.*, *J. Biol. Chem.* 136: 365. 1940; Baumann and Metzger, *Endocrinology* 27: 664. 1940). The alcoholic (hydroxylated) ketosteroids can be separated either by the application of succinic anhydride (Pincus and Pearlman, *Endocrinology* 29: 413. 1941) or by adsorption (Talbot, *et al.*, *J. Biol. Chem.* 139: 521. 1941). It is desirable that assays be made directly on the separated fractions. The significance of quantitative variations in various fractionated 17-ketosteroids remains yet to be determined. Similarly the presence of varying quantities of androgenically active ketosteroids requires further elucidation.

The determination of 'normal' values for urinary 17-ketosteroids has been complicated by variations in methods of extraction and assay. There appears to be a definite diurnal rhythm in both men and women (Reifenstein, *et al.*, Pincus, *J. Clinical Endocrinology* 3: 195. 1943) of such a nature that the lowest values are obtained for the period of sleep. The diurnal rhythm may be ruled out by taking full 24-hour samples. Even in such specimens marked individual differences appear which cannot always be attributed to such factors as age, weight, or other obvious physical factors. Children below the age of 6 excrete very small amounts of neutral 17-ketosteroids (0.1 mg. per 24 hours) with increasing excretion from 6 to 18 years when a more or less characteristic level is attained. There appears to be a decline in excretion in extreme old age. Among normal mature persons there is a sex difference (but with considerable overlapping). Twenty-four-hour values for women vary from 5 to 18 mg. when the Zimmerman reaction is applied to the crude neutral fraction, 3.5 to 15 mg., respectively, on its application to the ketonic neutral fraction. Corresponding values for men are 7 to 27 mg. and 5 to 23 mg., respectively. The alcoholic ketosteroids contribute from 50 to 85 per cent of these titers, the β-ketosteroids seldom exceed 15 per cent of the total titer and are ordinarily 2 to 3 per cent of the total.

Significant increases above normal have been encountered in cases of adrenal hyperplasia or adreno-cortical carcinoma (though exceptions to the latter have been noted) and in liver cirrhosis(?). Significantly low levels of excretion have been regularly encountered in Addison's disease and hypothyroidism. In conditions ranging from the common cold to almost any surgical intervention, marked temporary declines in urinary 17-ketosteroid excretion occur. The significance of these and numerous other variations in 17-ketosteroid excretion requires further investigation.

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EDITORIALS

EFFECT OF TISSUE INJURY ON THE BLOOD SUGAR LEVEL IN DIABETES MELLITUS

It has long been known that the hyperglycemia and glycosuria of the diabetic patient are accentuated by inter-current infection or trauma and that increased amounts of insulin are commonly needed to keep the patient in equilibrium under such circumstances. The mechanism through which the hyperglycemic effect is produced has remained until recently, however, a matter concerning which even plausible theory has been lacking. The problem has been under study by Menkin[1] during the past two years and data are now at hand for an explanation of the phenomenon.

Comparative observations were made on non-diabetic dogs and those which had been subjected to destruction of the pancreas. The method was to inject turpentine into the pleural cavity and withdraw the exudate for analysis for certain of its relevant constituents. These included sugar, total proteins, urea and lactic acid. By determining the same materials in the blood, any significant gradients as between the two sites could be recognized. In the control dogs, within the first few hours of the induced inflammation, the concentration of glucose in the exudate proved to be higher than that in the blood stream. The increased level of exudate sugar, however, was not sustained but soon dropped as low as, or even lower than, that of the blood sugar. Re-injection of the irritant induced a second rise in the blood sugar but this was also transient. Since at times definite elevation of the blood sugar occurred, the increase in the exudate could be ascribed in such instances to seepage from the blood into the irritated tissue. That this is not the whole explanation, however, is evident from the fact that the hyperglycemia was only transient whereas the augmented exudate sugar persisted. In contrast with the evanescent rise in the blood sugar of the normal dogs, the effect of similar inflammation in the diabetic subjects proved to be greater and longer sustained.

One possibility in explanation of the phenomenon would be that some of the turpentine had been resorbed from the pleural cavity and carried to the liver, thus bringing about augmented hepatic glycogenolysis. Since, however, the turpentine-induced inflammation was not accompanied by changes in the glucose-tolerance curve, as does occur after liver injury, Menkin regards that explanation as inadequate. He emphasizes the fact that throughout the duration of the inflammation the exudate sugar of the diabetic animal remains consistently at a higher level than does the blood sugar, and this in spite of the fact that glucose is extremely diffusible.

The explanation that best seems to fit the facts is, as Menkin says, that constant new formation of sugar occurs at the site of the tissue injury. A concomitant rise in the urea concentration of the exudate suggests that the source of the newly formed sugar is protein. It is the diffusion of the newly formed glucose into the circulating blood from the site of tissue injury that enhances the diabetic condition.

R.G.H.

[1] Menkin, V.: Gluconeogenesis and cellular injury. A further inquiry into the mechanism involved in diabetes enhanced by inflammation. *Am. J. Physiol.* 138: 396. 1943.

HORMONE FACTORS IN LIBIDO

Libido or amorous desire in the human being is a complex function in which anatomic, physiologic, neurologic, hormonal and psychologic factors all play determining parts.[1] States of ill-health aside, libido is either present or easily aroused in men at all times during the reproductive period of life, whereas in women it is much less constantly experienced. That destruction of the primary sex glands results in complete loss of libido is widely believed, but such is not necessarily the case in either men or women.

Strictly speaking, since libido is a subjective reaction, it can be studied convincingly only in human beings. To what extent arousal of mating behavior in infra-human forms can be equated with libido must remain conjectural, though 'willingness' or 'unwillingness' to mate certainly suggests the presence or absence of 'desire.' In certain animals, the female of the species will receive the male in coitus only when in heat or estrus and this is timed with follicle maturation. In many animals there is evidence that the administration of estrogenic substances to castrated females or to intact females outside of the mating season will awaken sexual receptivity. The period of heat in the bitch lasts for a little longer than one week and occurs at 6-month intervals. The administration of fairly large doses of pregnant mare's serum or of combinations of pregnant mare's serum and chorionic gonadotropin to bitches is capable of inducing estrus-like changes several months before the expected estrus so that in some instances the male will be received in coitus.[2] The follicle-stimulating effect of the gonadotropins not only increases estrogen production but probably accounts indirectly for minute amounts of progesterone. In the induction of sexual receptivity in the castrated guinea pig or rat it has been said that not only the estrogenic hormone but also progesterone is necessary.[3] Young and his collaborators[4] obtained more frequent and more normal responses in castrated guinea pigs if a little progesterone supplemented the course of estrogens.

The cycle of the female chimpanzee simulates that of the human female. Unlike the latter, however, the chimpanzee will accept the male only during the height of genital turgescence, which corresponds to the phase of follicle maturation. During the luteal phase, regressive changes set in, at which time the female will fight off the male. It may be said insofar as estrus is concerned, that the corpus-luteum hormone has an action opposite to that of estrogens. This fact receives further corroboration in the work of Gillman[5] who has shown that the perineum of the baboon is a sensitive indicator in experiments involving the use of female sex hormones. Deturgescence in the normal adult female baboon is a positive phenomenon, due to the presence of progesterone and not to the absence of estrogens. Progesterone administered in total doses of 10 mg. or less will cause depression of the turgescent perineum.

In case of the human species certain females exhibit even nymphomaniacal tendencies during the weeks before the onset of menses. These same individuals frequently show evidence of premenstrual tension. Endometrial biopsies often reveal imperfect progestinal types of endometrium and the blood-estrogen titers may be somewhat higher than normal. It may be that in these cases excessive estrogen over-rides corpus-luteum activity. A high threshold in the kidney for estrogen excretion may be the prime fault. Following the administration of parenteral progestins to these women in doses of 1 to 5 mg. every 3 to 7 days or oral progesterone in 5 mg. doses during the last half of the menstrual cycle, there is frequently noted a detumescence of the sexual urge.[6]

Although estrogens have been administered with resultant increase in libido, nevertheless many women without sexual desire fail to respond to even massive doses. The addition of small amounts of progesterone to the estrogen therapy or the administration of gonadotropins have evoked in some instances more satisfactory results in these patients in whom estrogens alone proved futile. More consistent results, however, are obtained with continued androgen therapy. Seventy-five to 200 mg. of testosterone propionate has frequently proved aphrodisiacal. Information as to the status of the sexual libido before and

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[1] Greenblatt, R. B.: *J. Am. Med. Assoc.* 121: 17. 1943.
[2] Greenblatt, R. B., and E. R. Pund: *South. M. J.* 34: 730. 1941.
[3] Allen, W. M.: In discussion of paper by Greenblatt[1].
[4] Young, W. and others: Quoted by G. W. Corner, The Hormones in Human Reproduction, Princeton University Press, 1942, p. 97.
[5] Gillman, J.: *Endocrinology* 26: 1072. 1940.
[6] Greenblatt, R. B., F. Mortara and R. Torpin: *Am. J. Obst. & Gynec.* 44: 658. 1942.

after implantation of pellets of testosterone propionate in dosages varying from 25 to 400 mg. was obtained from 55 women.[1] It was learned that restoration of libido readily occurred following implantation in those women who at some time had known libido. Many married women volunteered the information that the loss of sexual desire led to marital discord. Following pellet implantation there was a return of coital pleasure, which often terminated in orgasm. A reawakened interest on the part of the husband usually followed and husband and wife once more fell in love. Among those women who had a strong to moderate degree of sexual desire before implantation, either no significant change or further increase in sexual pleasure was noted. Two women with normal libido had a temporary decrease in sexual desire for several weeks immediately after pellet implantation and then a resurgence of the libido to a greater degree than that before the implantation. In several instances it was noted that the libido returned to the pre-implantation status by the end of the third to eighth month. In the majority, however, it persisted long after the pellets had been absorbed. In 3 women who had never experienced sexual desire no change was noted. Salmon and his associates[7] have studied the effects of testosterone propionate on the sexual reaction of women and concluded that androgens *a*) cause a heightened susceptibility to psychic and somatic sexual stimulation, *b*) produce an increased sensitivity of the external genitalia, and *c*) induce a greater intensity of sexual gratification.

The increase in libido in the woman following the administration of chemically pure androgenic substance in one form or another, must be the result of a specific pharmacologic effect. The action may be mediated through minor changes in electrolyte balance or the effect may be directly on specific organs. Hartman[8] noted that testosterone invariably had an estrogenic action on the sex skin of the female monkey. The sex skin was always brilliant red. In this respect he found progesterone antagonistic to estrin. Testosterone did not antagonize the action of estrogens. Even in pregnant macaques Hartman was able to blanch the sex skin with a sufficiently high dosage of progesterone. However, the concurrently injected estrogens and testosterone or both were sufficient to over-ride the blanching action of the progesterone.

Large doses of progesterone when administered parenterally or orally in the form of anhydrohydroxyprogesterone frequently have a depressing effect on woman's sexual desire. Repeated doses of desoxycorticosterone, like progesterone, also proved anaphrodisiacal. In a series of 23 women in whom pellets of progesterone were implanted for various gynecic disorders it was noted that in over one-half there was a decided depression of the sexual libido. This was particularly clear cut in several in whom sexual libido had been markedly exaggerated. Two patients, however, volunteered the information that the libido had increased.

In an ovariectomized woman of low intelligence, poor breeding and uninhibited instincts several instructive observations were made. Some time after castration she complained of marked decrease of sexual desire. It was found that libido was greatly heightened following the ingestion of alcoholic liquors or after the administration of courses of either estrogens or androgens. The administration of progesterone, however, caused a marked slump in libido, leaving her sexually nonreceptive. When pellets of 30 mg. of estradiol and 50 mg. of progesterone were implanted simultaneously libido was greatly enhanced.

From the inconsistent evidence now available a final over-all appraisal of the precise significance of hormonal factors in libido cannot be offered. Human behavior involves all sorts of mental processes not subject to experimental control. In women with normal libido, sexual gratification may depend mostly on the proper 'amatory prelude' or on the proper mechanics of coitus.[9,10] Sufficient evidence has accumulated to show that the administration to women of estrogenic and particularly androgenic substances in sufficient dosage may increase or awaken libido and that chemically pure progesterone and desoxycorticosterone in large dosage may suppress sexual desire. Altogether, it appears, then, that sexual libido is a phenomenon depending in part but not entirely upon well defined chemical substances.

R.B.G.

[7] SALMON, U. J.: In discussion of paper by Greenblatt[1].
[8] HARTMAN, C. G.: *Endocrinology* 26: 449. 1940.
[9] KELLY, G. L.: Sexual Feeling in Woman. Kingsport, Tenn. Kingsport Press, 1930.
[10] HUHNER, M.: Sexual Disorders. F. A. Davis Co., Philadelphia, 1942.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E.C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

BOOK REVIEWS

BÜNGELER, W., AND U. L. TORRES.

Das Relações da Osteodistrofia com a Hiperplasia das Paratiroides e Insuficiência Renal (Contribuição ao estudo das molestias osseas na lepra) (With Summary in English). *Empresa Grafica da "Revista dos Tribunais" LTDA, São Paulo,* 1942.

The authors introduce the work with a discussion of two of the most important skeletal disorders, osteitis deformans (Paget's) and generalized osteitis fibrosa (v. Recklinghausen's). The remainder of the book is concerned with the physiology and function pathology of the parathyroid glands. New investigations by the authors led them to the conclusion that parathyroid hyperplasia is commonly an adaptive reaction to primary disturbances elsewhere, and especially in the kidneys. It was found that induction of fibrous osteitis by the agency of metallic salts or of acids causes first chronic renal insufficiency followed by the skeletal changes. Similarly, clinical renal injury and especially that seen in leprosy is accompanied by similar change in the bones, the degree of kidney disturbance and of bone alteration running parallel. The association is mediated through the parathyroid glands.

The book is well printed and fully illustrated by excellent original photomicrographs.—*R.G.H.*

CHAVES, N.

As Adrenais Na Fisiologia Sexual, *Imprensa Industrial, Recife,* 1942.

The author presents a timely discussion of the relationship of the adrenal glands to the determination of sex and the endocrine functions of the gonads. The topic is treated systematically, considering the evidence at various levels, the embryologic and histologic, and physiologic and the clinical. A closing bibliography is made up of some 200 citations.—*R.G.H.*

ADRENALS

PATTERSON, J., I. M. MCPHEE AND A. W. GREENWOOD.

17-Ketosteroid excretion in adrenal virilism. *Brit. M. J.* 1: 35. 1942.

All cases of adrenal tumors and of primary virilism showed very high excretions of 17-ketosteroids and it was not possible to distinguish between adrenal hyperplasia and adrenal tumors before puberty on the basis of urinary excretion values. In secondary virilism only half of the patients showed increased 17-ketosteroid excretion rates, the others being normal. Three cases of feminism showed low ketosteroid excretion rates.—*D.A.M.*

SEMMEN, W.

The effect of adrenal cortical hormone (desoxycorticosterone acetate) on the blood composition in toxic diseases. *Ztschr. kinderh.* 62: 65. 1940.

Administration of desoxycorticosterone acetate to patients with severe toxic forms of diphtheria, scarlet fever and dysentery had no influence on the increased blood potassium or decreased blood sodium and chloride nor on the clinical course of disease.—*D.A.M.*

WILSON, A.

Sublingual desoxycorticosterone acetate in Addison's disease. *Lancet* 242: 762. 1942.

In 4 patients with Addison's disease, administration of 10–20 mg. per week of desoxycorticosterone acetate intramuscularly brought about satisfactory results. In the same patients, daily sublingual administration of 10 mg. in propylene glycol failed to maintain a satisfactory state.—*D.A.M.*

ENDOCRINE GENERAL

BENJAMIN, H. R., AND A. A. WEECH.

Basal heat production in relation to growth. A longitudinal study on normal infants six to twenty months of age. *Am. J. Dis. Child.* 65: 1. 1943.

A total of 217 observations, covering the entire age span, were made on two infants, and 40 additional observations covering shorter periods were obtained on two other infants. An open-circuit-type chamber calorimeter was used. Large day to day fluctuations in the basal heat production of individual infants were observed, with greater variation in a given infant during the early months of life. In terms of the coefficient of variation the fluctuations amounted to 9 per cent, as compared with a reported 5 per cent for adults. In relation to growth, the association between total calories and body weight was the closest, and there was no evidence of change in the calories produced per kilogram with advancing age. In contrast, there was a definite change with growth in the heat production per unit of surface area or per unit of height. However, the quantity of heat produced per kilogram of body weight varied significantly in different infants of the same age. Day to day fluctuations limit the accuracy with which basal heat production can be predicted from measures of growth. Over the age span studied, prediction on the assumption of a constant heat output per kilogram of weight is not significantly less accurate than prediction on the basis of regression equations. For this study and in other reported studies there was found a range of 11.3 to 13.7 per cent in the total error of prediction, composed of variability among different infants (6.5 to 9.8 per cent), and longitudinal variation in the individual infant (5.5 and 10.3 per cent). No evidence was adduced that the excess heat production per kilogram of tissue of the infant over that of the adult is due to the normal changes in the rate of growth.—*E.C.R.,Jr.*

BURROWS, H., D. H. MACLEOD AND F. L. WARREN.

Excretion of ketosteroids in human pregnancy urine in relation to sex of the fetus. *Nature, London* 149: 300. 1942.

Ketosteroids were estimated colorimetrically. Results were not conclusive. Although women bearing male feti excreted more ketosteroids, there was a wide range of individual values.—*D.A.M.*

CAMERON, D. E., D. MELE, H. S. HIRST AND F. FELDMAN.

Abnormal brachial blood pressure response to postural change in patients suffering from psychoses of the senium. Control by thyroid. *Psychiat. Quart.* 17: 67. 1943.

Forty-one senile patients and 16 normal controls were tested on a tilt-board for circulatory compenstatory efficiency. The scores of the seniles were markedly inferior to those of the control subjects. Ten of the patients were treated with desiccated thyroid substance, 3 grains daily. In 7 of these the compensatory efficiency was improved.—*R.G.H.*

DRIPS, DELLA G.

Relation of sex hormones to the climacterium. *Jour. Lancet* 62: 437. 1942.

A review.

DICKINSON, R. L.

Gynecology and psychiatry. *Bull. Menninger Clin.* 7: 3. 1943.

The author contributes a brief introduction to a number of the Bulletin that is devoted exclusively to psychological and psychiatric aspects of gynecology and obstetrics. He emphasizes the need for more intensive attention to the psychosomatics of these subjects.—*R.G.H.*

DIAZ MINDURRY, EUGENIO F.

Hormone treatment of nervous heart disease. *Semana méd.* 49; ii: 1230 (1942).

A few cases are reported of cardiac disturbances of indubitably neurotic character in which the neurosis was based on endocrine disturbances. The general symptoms were usually tachycardia, palpitations, extrasystoles, precordial pain. One patient developed these symptoms after taking care of her mother, suffering from heart disease and copied her complaints. The treatment, more or less successful in every case, consisted in a case of artificial menopause, in estrogens and stilbestrol, in premenopause with myoma of the uterus and a tendency towards hypermenorrhea, in testosterone, in amenorrhea, estrogen and desoxycorticosterone and in a mild hyperthyroidism secondary to a moderate hypogonadism, with diiodotyrosine, and insulin; the latter was later substituted by estrogens.—*A.E.M.*

FITZGERALD, J. E., AND AUGUSTA WEBSTER.

Obstetric significance of barbiturates and vitamin K. *J.A.M.A.* 119: 1082. 1942.

In a series of over 600 cases in the Cook County Hospital, Illinois, it was found that the administration of vitamin K, either the original alfalfa extract or the synthetic product, to a mother in labor increases the percentage of prothrombin of both mother and child. The vitamin may be given either orally or parenterally. Such medication also prevents the drop in the prothrombin level of the baby which normally occurs from the second to the fifth day. The administration of sodium pentobarbital or sodium amyl bromoallyl barbiturate as an analgesic definitely decreases the prothrombin level in mother and child. The decrease can be prevented by the administration of vitamin K to the mother during labor. It is apparent that even small doses of barbiturate affect the prothrombin level.—*C.C.P.*

FRANKEL, L.

Endocrinology and the specialties. *Rev. méd. de Rozario* 32: 1002. 1942.

Endocrinology as a clinical specialty is discussed in regard to its development and relation to internal medicine, obstetrics and gynecology.

GILL, M. G.

Functional disturbances of menstruation. *Bull. Menninger Clin.* 7: 6. 1943.

The psychological meaning of menstruation is discussed in the light of folk superstitions and current lay misapprehensions. The psychological etiology of many cases of amenorrhea and dysmenorrhea is pointed out and various cures by psychotherapy are mentioned. It is emphasized that the gynecologist must, for the most part, serve as his own psychiatrist and that, as such, he can frequently do much to ameliorate menstrual disorders.—*R.G.H.*

HOSKINS, R. G.

Psychosexuality in schizophrenia—some endocrine considerations. *Psychosom. Med.* 5: 3. 1943.

Numerous features of the schizophrenic psychosis point to an immature level of psychosexual functioning. The question is raised whether this is due to deficiency of sex hormone. It is pointed out that sexual behavior in animals is largely determined by this factor: mating activity can be prevented by castration and precocious sex behavior can be induced by the use of primary sex hormones. The schizophrenic patient, however, usually has normal genitalia and probably excretes sex hormone in an approximately normal amount. Furthermore, castration in human beings seldom if ever gives rise to schizophrenia. nor does that operation have much influence on the psychosis if performed after its development. Although quantitative alterations in the sex hormone titre show little correlation with the psychosis it is theoretically possible that variations in responsivity to the hormones might be a factor. That such responsivity varies widely under different conditions is well known. Dissociation between the somatic and the psychodynamic reactions to sex hormones is also possible under numerous conditions, e.g., precocious puberty in boys and girls is commonly not accompanied by much eroticism. Dissociation between sex hormone production and mating response can be demonstrated experimentally by the induction of lesions in the hypothalamus. Another theoretical possibility is that schizophrenia might be induced by imbalance in the titres of circulating androgen and estrogen as homosexuality is believed by some to be produced. This possibility is controverted by the infrequency with which administered sex hormone benefits homosexuality and by the fact that acquired sex reversal in man does not lead to schizophrenic symptomatology. Whether or to what extent schizophrenia might be due to qualitative abnormalities of sex hormone production is discussed. Evidence is cited that certain animals are more responsive in terms of sex behavior to stallion-urine extract than to testosterone. Evidence of aberrant sex hormone production in man is, however, lacking. Likewise lacking is evidence that the psychosexual perturbations of schizophrenia might be due to abnormalities in the metabolism of normal sex hormone. It seems probable that the psychosexual disharmony of schizophrenia is not to be ascribed therefore to immediate abnormality in either amount, balance or chemical nature of the sex hormones. The possibility remains that abnormal responsivity to these hormones might account for the psychosis and that successful normalization of the responsivity might be an effective therapeutic procedure.—*Author's Summary.*

KARNAKY, K. J.

The use of stilbestrol for the treatment of threatened and habitual abortion and prema-

ture labor: a preliminary report. *South M. J.* 35: 838. 1942.

Uterine pain of threatened, habitual, complete and incomplete abortion, and normal labor pains can be stopped immediately by giving 25 to 200 milligrams of stilbestrol in oil into the anterior wall of the cervix. Hard contracted uteri of abortions can be made to soften and assume normal consistency within 30 to 60 seconds, and will remain so for from 6 to 24 hours. Stilbestrol taken orally can be used to carry habitual abortion cases to term, and to stop labor pains and vaginal bleeding in cases of threatened and habitual abortion. Stilbestrol has caused no *in utero* deaths in 20 cases of normal pregnancy. Normal children have been born to 33 mothers who have received large doses of stilbestrol because of threatened, habitual abortion, or premature labor. Stilbestrol taken orally does not produce nausea in the pregnant woman, and, apparently, prevents morning sickness.—*H.W.*

KERMAN, E. F.

Testosterone therapy of involutional psychosis. *Arch. Neurol. & Psychiat.* 49: 306. 1943.

Twelve men were carefully selected as permitting an unequivocal diagnosis of involutional melancholia. They were observed for considerable periods to rule out the probability of spontaneous improvement. Courses of testosterone propionate in oil in dosage of 25 mg. were given twice weekly for thirteen weeks. After two months a second seven weeks' treatment was begun. In only a single instance did any significant degree of improvement occur.—*R.G.H.*

KING, J. K.

Roentgen therapy to the pituitary gland in functional disturbances of and associated with menstruation. *South M. J.* 35: 616. 1942.

This report is based on a study of 230 patients who were treated by roentgen irradiation of the pituitary gland for functional disorders of endocrine origin, manifested by disturbances of the menstrual cycle, headaches, nervousness, fatigue, subnormal sex life, sterility, low metabolic rate and abnormal weight. No hormonal assays on these patients are reported, and thyroid substance is the only hormonal therapy employed. Of 230 patients, ranging from 12 to 47 years, 105 were completely relieved, 61 were improved, 19 were not benefited and 45 were not followed. Excessive bleeding is most amenable to pituitary irradiation, while amenorrhea due to secondary glandular dysfunction responds favorably in many cases. Irradiation can do nothing for hypomenorrhea or dysmenorrhea unassociated with other symptoms, although if either are merely one feature of this syndrome correction may be expected in about 50% of the cases. Irradiation also has a beneficial effect on the fertility and sex life of the patient.—*H.W.*

KNIGHT, R. P.

Functional disturbances in the sexual life of woman. *Bull. Menninger Clin.* 7: 25. 1943.

An instructive discussion of the sociology, psychology, prophylaxis, mental hygiene and treatment of sexual anxiety and frigidity.—*R.G.H.*

LATIMER, J. K.

The action of testosterone propionate upon the kidneys of rats, dogs and men. *J. Urol.* 48: 778. 1942.

Treatment of rats and dogs with testosterone propionate produced a renotrophic effect, which was a true increase in tissue solids, due to an increase in cytoplasm. Renal function in dogs, measured by inulin clearance and diodrast time, could be increased by testosterone propionate, in proportion to the increase in renal tissue. In humans, the largest safe dose improved renal function only when combined with the compensatory hypertrophy following nephrectomy. From autopsy reports, the kidney weight/body weight ratio of 50 adult, sexually active, human males was significantly higher than that of 50 adult, sexually active human females. One hundred infants showed no sex difference. Blood pressure showed no significant change under this treatment with testosterone propionate, in rats, dogs or humans.—*H.W.*

MCCUNE, D. J., H. H. MASON AND H. T. CLARKE.

Intractable hypophosphatemic rickets with renal glycosuria and acidosis (Fanconi syndrome). Report of a case in which increased urinary organic acids were detected and identified, with a review of the literature. *Am. J. Dis. Child.* 65: 81. 1943.

In this 9 year old boy the chief features were: (1) severe hypophosphatemic rickets, renal glycosuria, and extremely reduced serum bicarbonate; (2) moderate polyuria, albuminuria and cylinduria with normal nonprotein nitrogen and urea; (3) acid urine with huge amounts of ammonia and organic acids; (4) slightly reduced

serum sodium and fixed base; (5) excessive urinary phosphorus and calcium during a balance study; (6) normal sodium, chloride and magnesium metabolism; and (7) no obvious effect from 5,000 U.S.P. units of vitamin D daily for several weeks. Other therapeutic recommendations were not carried out; the patient died; no autopsy was performed. The authors identified, for the first time, the organic acids: 82 per cent amino acids, 11 per cent lactic acid and 7 per cent betahydroxybutyric.

The data were interpreted to indicate diminished ability of the renal tubular epithelium to resorb dextrose, amino acids and phosphate from the glomerular filtrate. Inasmuch as the requirement of cation to neutralize the organic acids was still not satisfied by the production of a highly acid urine, of large amounts of amonia and of increased urinary volume, mineral cations of the body fluids were called on, with resultant depletion of fixed base. Recurrent hypoglycemia was thought to be responsible for the excretion of betahydroxybutyric acid. The presence of lactic acid was ascribed hypothetically to either renal tubular or hepatic dyscrasia.

Thirty similar cases have been reported in the last 15 years. Hypophosphatemia was demonstrated in 17 of these; in 3 the serum phosphate was elevated; in 10 it was not determined. In 4 other instances excessive amounts of urinary organic acids have been recognized but not identified. Eleven autopsies have been made. Pathologic changes have been most consistently found in the kidney, with serious involvement of the tubular epithelium more often than of the glomeruli. In a few cases the liver has shown changes varying from focal necrosis to cirrhosis. Four cases (possibly another) showed deposits of crystalline cystine throughout the reticuloendothelial system. Cystinosis may have been overlooked in other cases.

The syndrome bears the name of Fanconi, who postulated in 1931 that the symptoms developed because of a hereditary inadequacy of the renal tubular epithelium which allowed dissipation of dextrose and cations. The authors believe that the additional data accumulated since then support the concept of a renal origin for the syndrome, but favor a defect in the tubular resorption of phosphorus rather than of cation. They consider this syndrome one phase or aspect of a larger morbid series which merges imperceptibly on one side with classic hyperphosphatemic renal rickets and on the other with the poorly-understood, so-called "cystine rickets."—*E.C.R., Jr.*

MENNINGER, W. C.

The emotional factors in pregnancy. *Bull. Menninger Clin.* 7: 15. 1943.

An attempt has been made to touch on the more important psychological stresses and strains associated with pregnancy and a few of the manifestations of these. The universality of pregnancy and its importance as one of the major experiences in the life of a woman, both psychologically and physiologically, justify an extensive study from the psychosomatic point of view. Such a study should encompass the attitudes of women, both married and unmarried, towards pregnancy in terms of their individual life experience and situation. Such a study should also include the close cooperation of the obstetrician and psychiatrist in the investigation and management of a large number of pregnant women through the entire course of the pregnancy. And finally, the study should include a close investigation of women during the post-partum state—the woman's struggles with herself and her husband and her baby. Such an approach should be extremely fruitful as a source of material which might be used to aid psychological and physiological adjustment to the reproductive process.—*Author's Summary.*

MENNINGER, K. A.

Emotional factors in organic gynecological conditions. *Bull. Menninger Clin.* 7: 47. 1943.

It is suggested that emotional factors demand consideration even in those cases in which organic pathology is obvious. A case is presented in which there was evidence that emotional factors determined a fatal uterine hemorrhage. Possible mechanisms are discussed whereby connection can be traced between emotional factors and structural disorders such as hypotonicity of the pelvic muscles, leading to prolapse, asthenic dystocia and obstetrical laceration. The relation of emotional factors of possible significance to fibromyomata, endometritis and false pregnancy is briefly discussed.—*R.G.H.*

NIXON, W. C. W., MARGARET D. WRIGHT AND E. C. FIELLER.

Vitamin B_1 in the urine and placenta in toxaemia of pregnancy. *Brit. Med. J.* 1: 605. 1942.

Urine analyses and placental analyses were made for vitamin B_1 by the assay method in a series of 106 pregnant women among hospital populations. It was found that in cases of eclampsia the amount of vitamin B_1 excreted in the

urine on admission to hospital was significantly lower (0.94 I.U.) than in normal pregnancies (3.39 I.U.). The concentration of the vitamin was also lower in pregnancies accompanied by eclampsia (5.9 I.U.) than in normal pregnancies (19.4 I.U.). —*D.A.M.*

PEARLMAN, W. H., AND G. PINCUS.

The metabolism of estrone in men. *J. Biol. Chem.* 147: 379. 1943.

Massive doses of estrone, as the acetate, were injected into 7 young men. From the strong phenolic fraction of the urine collected for 96 hours following injection, there was recovered a small amount of crystalline estriol. An exogenous origin of the estriol isolated is precluded. The high concentration of estrogenic activity in the weakly acidic, phenolic, non-ketonic fraction is due chiefly to α-estradiol. This is substantiated by the changes in the activity of this fraction after the application of mild oxidative procedures.—*Author's Summary.*

SHUTE, EVAN.

Vitamin E and premature labor. *Am. J. Obst. and Gynec.* 44: 271. 1942.

A series of 46 cases of threatened premature labor in the author's private practice were treated prophylactically with vitamin E in the form of wheat germ oil or ephynal. Sixty-seven per cent were taken to term with delivery of live children. —*E.C.H.*

SIMPSON, S. L.

The increasing importance of endocrinology in general medicine. *Brit. M. J.* 27: 247. 1943.

The author reviews the manifestations of endocrine diseases in various branches of medicine including surgery and gynecology. He concludes that an Endocrine Clinic should be an integral part of a hospital and should serve as a model for modern methods of investigation, research and therapy in disease.—*R.B.G.*

VICKERS, V. S., AND H. C. STUART.

Anthropometry in the pediatrician's office. Norms for selected body measurements based on studies of children of north European stock. *J. Pediat.* 22: 155. 1943.

The authors present 21 tables of normal values for body weight, head circumference, chest circumference, chest breadth, body length (recumbent and standing), pelvic breadth (recumbent and standing), crown-rump length, sitting height, and growth increments compiled from measurements they have made on Boston boys and girls between the ages of birth and 10 years. The values for each sex are based on data from 140 children at birth, and from progressively smaller groups at succeeding ages to 25 at 10 years. The medians and certain other percentiles, the extremes of the series, the means and sigmas are given. Standard measurements and the techniques for obtaining them are defined.—*E.C.R.,Jr.*

WETZEL, N. C.

Assessing the physical condition of children. I. Case demonstration of failing growth and determination of "Par" by the grid method *J. Pediat.* 22: 82. 1943.

The author has devised a chart or "Grid" to appraise objectively the growth and development of children from the plotted record of their age, height and weight. The technique of appraisal involves the evaluation of physical status in terms of physique, developmental level and nutritional grade at every point, and the evaluation of physical progress from point to point. One case is reviewed in detail to illustrate the principles and the method of analysis.—*E.C.R.,Jr.*

WETZEL, N. C.

Assessing the physical condition of children. II. Simple malnutrition: A problem of failing growth and development. *J. Pediat.* 22: 208. 1943.

The author applies his "Grid" to the problem of malnutrition and demonstrates how it can be utilized to detect conditions of failing growth and development and to evaluate their response to suitable therapy. One case is analyzed to illustrate the procedure.—*E.C.R.,Jr.*

WRIGHT, C. A., AND E. H. WILLIAMS.

Endocrine therapy in dementia praecox. *M. Rec.* 156: 28. 1943.

Certain types of psychic abnormalities are accompanied by endocrine dysbalance. In the male homosexual the androgen-estrogen ratio decreases, in the female it increases. In dementia praecox, there is a deficiency of the homogenous hormone, without a rise in the heterogeneous hormone, as well as other endocrine deficiencies. Treatment with massive doses of the deficient hormones, as determined by assays, may help the mental abnormalities. Five illustrative cases

of dementia praecox accompanied by endocrine deficiencies are given. Two females were treated with estrogens, one male with androgens, a hypopituitary male with androgen and gonadotropins, and a hypoadrenal male with adrenal cortex extract. In all cases cited, remission of the mental symptoms occurred.—*H.W.*

GONADS

ALYEA, E. P., AND A. F. HENDERSON.

Castration for carcinoma of the prostate: a report of the immediate results. *J. Urol.* 48: 673. 1942.

Forty patients with carcinoma of the prostate were castrated. All showed immediate general improvement, with relief of metastatic pain. In 8 out of 26 patients there was an elevation of serum acid phosphatase, which dropped with castration or estrogen therapy. X-rays showed an increase of bone healing and disappearance of metastases. In 30 patients who returned for examination the prostate was markedly reduced in size. Stilbestrol is indicated in cases not responding satisfactorily to castration and to relieve hot flashes.—*H.W.*

AUB, J. C., AND S. S. KETY.

Recent advances in testosterone therapy. *New England J. Med.* 228: 338. 1943.

The physiology, methods of administration and indications for testosterone therapy in diseases peculiar to the male, gynecologic conditions and in general diseases are reviewed. The authors conclude "There is as yet no evidence of permanent harm resulting from its moderate and clearly indicated usage."—*R.B.G.*

BICKERS, W.

The placenta: a modified arteriovenous fistula. *South M. J.* 35: 593. 1942.

The circulatory changes occurring in pregnant women, particularly the fall in the arteriovenous oxygen difference, the marked elevation in the venous pressure of the lower extremities, and the arteriovenous bruit heard over the placental site, can be explained by assuming that the placenta is an arteriovenous fistula. Studies of the venous pressures in both femoral veins and an arm vein, the appearance of edema, and, after delivery, the placental site, were made during pregnancy, and through delivery, on 23 patients. The highest femoral venous pressure recorded was that of 260 mm., in a case with central placenta previa. The pressures in the legs exceeded those of the arms in all females studied with a mean of 108 mm. In 12 of the patients with anterior or posterior placental sites the venous pressures in both legs were about equal, with equal swelling in both ankles. In 11 patients with lateral placental sites, the femoral venous pressure and the edema were greatest on the side of placental implantation. Blood shunted from the uterine artery to the uterine vein on the side of implantation would transmit an increased pressure to the femoral vein.—*H.W.*

BISCHOFF, F., AND G. J. CLARKE.

Influence of nephrectomy on ovarian response to gonadotropins. *Am. J. Physiol.* 138: 241. 1943.

Greater ovarian weights were produced in partially nephrectomized rats than in intact animals, by equivalent amounts of gonadotropins. Augmentation after sheep pituitary substance was of low magnitude and, after pregnant mare-serume hormone, may have been accounted for by loss of body weight following operation. The response to prolan, however, was so greatly augmented in the nephrectomized rats (ovarian weight increase: 175 to 240% of that in the intact animals) that this result is regarded as significant. The author suggests that the normal refractoriness toward prolan is a result of a low renal threshold for this hormone.—*J.W.E.*

CHUTE, R., A. T. WILLETTS AND J. F. GENS.

Experiences in the treatment of carcinoma of the prostate with stilbestrol and with castration by the technique of intra-capsular orchidectomy. *J. Urol.* 48: 682. 1942.

Twenty-six of 27 cases of inoperable carcinoma of the prostate, treated by surgical castration, or a combination of surgical castration with stilbestrol therapy, showed rapid relief from pain of metastases, when present, great improvement in appetite and general health, and reduction in size and induration of the prostate with improvement in ability to urinate in most cases. Quickest and most satisfactory results were obtained by castration followed by the injection of 10 mg. of stilbestrol per day for 5 to 10 days. When stilbestrol alone is used, patients have to be kept on a maintenance dose of 1–3 mg. per day. No beneficial effect was noted on bony metastases. If elevated the acid phosphatase level fell towards normal after therapy, while the alkaline phosphatase usually rose. 17-ketosteroid determina-

tions were made in 18 cases before and after castration. In all but 4 cases the value fell immediately after castration. In these 4 cases the acid phosphatase decreased, and the patients did well clinically, while the 2 patients who did worst had values that fell after castration. The authors' impression is that the 17KS level does not give information of value as to the progress of disease in cases of carcinoma of the prostate. The technique of intra-capsular orchidectomy presented has certain cosmetic advantages in retaining a semi-normal appearance of the scrotum.—*H.W.*

DEAN, A. L., H. Q. WOODWARD AND G. H. TWOMBLY.

The endocrine treatment of cancers of the prostate. *J. Urol.* 49: 108. 1943.

Results of endocrine treatment of 60 patients for carcinoma of the prostate are presented. Thirty-four were surgically castrated and, in all but 2 cases, showed marked relief of symptoms. Eight treated with 2–5 mg. of stilbestrol daily showed improvement as great, though slower, as that obtained from orchiectomy. Stilbestrol is also beneficial when relapses occur following surgical castration. In 19 out of 26 patients the elevated serum acid phosphatase fell after castration to values slightly above normal, while 2 patients who showed no significant change had no clinical improvement after operation. Stilbestrol produced similar changes. Castration elevated the serum alkaline phosphatase in 12 of 26 patients, with marked increase in the degree of osteoplasia. Twenty-seven of 35 treated by bilateral orchiectomy showed mean preoperative levels of 16.6 mouse units of estrogen and 6.1 mg. of 17-ketosteroids per 72 hours. In all but one of these there was a post-operative drop of estrogen excretion to a mean of 8.5 mouse units. The 17KS output of 16 patients rose in 11 patients and fell in 5, after castration. Eleven of 16 patients on whom gonadotropic hormones were determined showed definite post-castration rises, while 5 had amounts too low to measure before or after operation. In 12 patients primarily treated with stilbestrol the 17KS excretion fell from a mean of 8.9 to 5.4 mg., while the estrogen excretion rose, presumably due to stilbestrol excretion. Castration apparently frees the anterior pituitary from testicular control, as shown by increased gonadotropic hormone excretion and increased adrenal stimulation, causing a rise in 17-ketosteroid output. Stilbestrol inhibits the anterior pituitary, causing a fall in the excretion of gonadotropin, and 17-ketosteroids. Both procedures cause marked clinical improvement, suggesting that the gonadotropic hormone from the pituitary is not directly concerned.—*H.W.*

DIAZ, J. T.

Pseudohermaphroditism. *Am. J. Dis. Chid.* 65: 67. 1943.

The case is reported of a child, aged 7½, who was angular in build; had long head hair; a normal voice; normal breasts; no facial or axillary hair; pubic hair 3 to 5 cm. long, which had been present for 3 years; a phallus 3 cm. in length and 1.8 cm. in diameter, which was held down by a thin membrane extending from the fenulum to the base and attached to the midline of the perineum; an external urinary meatus at the base of the phallus; no vaginal opening; two structures resembling labia majora on each side of the perineum; absence of testes in these structures or in the inguinal canals; no prostate; and an almond-sized mass on rectal examination which was thought to be a uterus. The child was being brought up as a girl. The author considered the patient to be a cryptorchid male child with hypospadias because chorionic gonadotropin (antuitrin S) 500 rat units intramuscularly twice weekly for 5 weeks caused an increase in the phallus to 4.1 cm. in length and to 2.4 cm. in diameter. The author postulated that in a male, gonadotropin would stimulate the interstitial cells of the testes to produce androgen which in turn would cause an increase in the size of the phallus; in a female, gonadotropin would have no definite effect on the external genital structures. He proposed this biologic test with gonadotropin as an aid in determining the functional nature of the gonads of patients whose sex is not apparent. No operation was performed.—*E.C.R., Jr.*

GILBERT, J. B.

Studies in malignant testis tumors. VIII. Tumors in pseudohermaphroditism: review of sixty cases and a case report. *J. Urol.* 48: 665. 1943.

Sixty cases of pseudohermaphrodites with testicular tumors, and one additional report, are reviewed in this paper, comprising about 1 per cent of the testis tumors studied in detail. There were 38 unicellular tumors (seminoma); 14 teratoma, and 9 miscellaneous or "malignant" tumors. These tumors were located in the scrotal testis twice, in the inguinally retained testis 8, and in the abdominally retained testis 48 times. In 8 patients both gonads were involved. Forty-

one patients were considered primarily operable, 11 had operations performed in spite of metastases while 9 were considered inoperable. Four patients survived 5 years or more, 3 with unicellular tumors, and 1 with a teratoma. In the bilateral testis tumors there were 4 unicellular, 3 teratoma, and 1 adenoma. In the entire group, only 4 Aschheim-Zondek assays were performed, and these were found to be negative. No androgen or estrogen assays were made. The 52 noninvolved gonads were located in the scrotum 3 times, in the perineum once, in the inguinum 8 times, and in the abdomen 38 times. Inguinal hernia was present in 12 patients; in some patients it may be the only lead to the identification of pseudohermaphroditism.—*H.W.*

HECKEL, G. P.

Pregnanediol excretion in normal women. *New York State J. Med.* 42: 2103. 1942.

Sodium pregnanediol glucuronidate excretions (24 hour urines) were determined at weekly intervals during pregnancy in 5 women and during normal cycles in 3 women. Curves of excretion are similar to those reported by others. Variations of considerable magnitude were noted.—*D.A.M.*

JOHNSON, W. O.

Vaginal biopsy studies after total hysterectomy. *South M. J.* 36: 23. 1943.

Studies of vaginal biopsies, from 4 months to 6 years after total hysterectomy, are reported on 60 patients. There is evidence of continued estrogenic effect upon the vaginal mucuous membrane up to 4 years after operation. Those patients who had lowered ovarian function at the time of operation had a more senile type of vaginal mucosa than the others in the group. Most marked changes occurred in two cases where radium had been used for cancer, and where castration had been perform ed prior to hysterectomy.—*H.W.*

LAPIN, J. H., W. KLEIN AND A. GOLDMAN.

Cryptorchidism. *J. Pediat.* 22: 175. 1943.

Thirty–nine of 200 boys treated at the Bronx Hospital have been followed since treatment for 2 to 9 years. Of these, 14 cases (35.9%) were at first considered to have responded successfully, but later this group was reduced to 6 cases (15.3%) by the omission of two patients in whom descent of the testes occurred without treatment, two patients in whom the descent was only partial, and four in whom hypogonadism ensued. The failures are analyzed. Therapy consisted of varied amounts of chorionic gonadotropin; testosterone propionate and thyroid in addition were employed too infrequently to warrant analysis. From these cases and a review of the literature, the authors concluded: (1) treatment for cryptorchidism should not be instituted until the patient was 14 years old, but then was advisable to relieve the deficiency of androgenic hormone formation and of spermatogenetic activity, and the psychologic handicap; (2) a preliminary test with endocrine therapy should be made in every case (except those with ectopic testes complicated by a substantial hernia in whom operation was inevitable), with the understanding that if the test failed to produce descent, the patient would be operated without delay to avoid the damage that the high abdominal temperature can do to testes that have become partially developed by therapy; (3) for this test chorionic gonadotropin is the only medication free from theoretical objections, providing it is given in a dosage not exceeding a total of 6,000 international units divided into frequent small doses during 6 weeks; and (4) a similar 6-week course of chorionic gonadotropin should be given immediately after operation to induce further testicular development.—*E.C.R.,Jr.*

LESSER, M. A.

Treatment of angina pectoris with testosterone propionate. *New England J. Med.* 228: 195. 1943.

Twenty-one men and one woman with angina pectoris were treated with testosterone propionate. The favorable results previously reported by the author (24 cases) were again obtained. Four patients were studied by means of exercise tolerance before and during the course of therapy to obtain quantitative measurements of their improvement. The amount of exercise before the development of an anginal attack was markedly increased under testosterone therapy and the severity of attacks was correspondingly diminished. Medication was administered in 25 mg. doses every second to fifth day for a total of 5 to 25 injections. An average of 28 days elapsed before quantitative improvement was noted and a period of 43 days before this improvement was marked. The duration of beneficial effects of testosterone propionate therapy varied with the individual. The shortest period of benefit was 2 months and the longest period of relief from anginal attacks was 18 months.—*R.B.G.*

MILLER, M. L., AND R. A. MOORE.

Variation in the daily urinary excretion of androgens in relation to benign hypertrophy of the prostate. *J. Urol.* 48: 544. 1942.

The capon comb growth assay was used to study the daily androgen excretion, for a period of 30 days, of 4 men in the 8th decade, 2 with benign hypertrophy of the prostate, 1 normal, and one with an atrophic prostate. No significant differences were found in the coefficients of variation of these patients.—*H.W.*

POLLOCK, W. F.

Histochemical studies of the interstitial cells of the testis. *Anat. Rec.* 84: 23. 1942.

Substances with chemical properties of the known active steroids of the testis were found in the interstitial cells of cats and other common laboratory mammals. No like substances were detectable in other parts of the testis. Thus histochemical data support physiological evidence that interstitial cells are the source of testicular androgen.—*J.W.E.*

PORTNOY, L.

The diagnosis and prognosis of male infertility; a study of 44 cases, with special reference to sperm morphology. *J. Urol.* 48: 735. 1942.

Forty-four males, with a history of barren marriage of 1 year or longer, are presented. In 16 of these the seminal fluid was normal in all respects. Successful conceptions occurred later in 7 of these cases, 3 following treatment of the female partner. In 14 cases of subfertility, with oligozoospermia associated with asthenozoospermia and defective morphology, and 14 cases of sterility, with complete azoospermia, or very marked oligozoospermia and defective morphology only 1 conception occurred subsequently. Twelve of these men were given treatment to improve spermatogenesis, with no significant improvement in the seminal fluid, and no success in establishing pregnancy. The prognosis of male infertility, with or without treatment, is quite poor. A detailed method of assaying male fertility is presented, with classifications and illustrations of sperm morphology.—*H.W.*

SCHONFIELD, W. A., AND G. W. BEEBE.

Normal growth and variation in the male genitalia from birth to maturity. *J. Urol.* 48: 759. 1942.

Measurements were made and reported on the genitalia of 1500 normal white boys. Relaxed and stretched penis length and circumference were measured directly. Testicular volume was estimated by comparison with a series of models of known volume. A high correlation was found between stretched and erect penis length. Cumulative frequency curves and growth curves, by age, are given for all factors measured. Growth curves for length and circumference show some pre-pubescent growth, followed by a marked increase during pubescence. Testis volume shows no change until pubescence when a phenomenal growth starts, somewhat earlier than that of the penis. Chronological age is an unreliable guide to genital development after age ten, but no better one can be suggested. Genital growth is a pubescence phenomenon, far outstripping measurements such as height and weight. The testicular volume changes so markedly with pubescence that it may be employed for determining its onset.—*H.W.*

TAYLOR, N., AND R. L. SCHAEFER.

Non-neoplastic hypergenitalism. An analysis of seventeen cases. *Psychosom. Med.* 5: 10. 1943.

A brief review of the literature includes an outline of the known causes of hypergenitalism and notes on theoretical considerations. Seventeen cases of non-neoplastic hypergenitalism are analyzed with respect to physical, psychological and social findings. A composite description of this endocrine type is presented. No treatment is suggested but understanding of the problem is essential for all who manage juveniles and adolescents.—*Author's Summary.*

BRONSTEIN, I. P., J. A. LUHAN AND W. B. NAVRELIS.

Sexual precocity associated with hyperplastic abnormality of the tuber cinereum: Report of a case. (Abstract). *Arch. Neurol. & Psychiat.* 48: 1022. 1942.

A girl 22 months of age exhibited vaginal bleeding, enlarged breasts and vulval hair. The possibility of involvement of the hypothalamic apparatus was entertained. Intracranial symptoms were not present. In pneumoencephalographic studies, visualization of the ventricles and cisterns revealed nothing abnormal. The child died of meningitis. A detailed postmortem examination was made. In the region of the tuber cinereum a globular, grayish white, glistening mass, about 4 mm. in diameter, was observed in the midline just in front of the mammillary

bodies. The pineal body appeared normal. Histologic examination of the tumor showed that it resembled in structure the tuber cinereum, and the diagnosis of a hyperplastic malformation (hamartoma in the sense of Albrecht's definition) rather than of ganglioglioma or pseudoheterotopia. The pituitary presented relative hyperplasia of the eosinophils of the pars distalis. Except for these alterations, the endocrine system was normal to macroscopic and microscopic inspection. The relation of the mass to the sexual precocity is discussed. Various mechanisms that might be responsible for this phenomenon are postulated. —*R.G.H.*

MARQUES, R. J.

Hypophysis and pigmentation. *Neurobologia* 5: 1. 1942.

Extensive pigmentary disturbances in 2 patients were attributed to dysfunction of the pituitary gland, in view of a singular genital anomaly in the one case and the fact that the anterior and posterior clinoid processes were joined by a bony ridge in the other. Therapeutic results are discussed.—*Author's Summary.*

MCLAREN, H., AND M. MCLEOD.

Diabetes insipidus in pregnancy. Case. *J. Obst. and Gynaec. Brit. Emp.* 49: 51. 1942.

Onset of diabetes insipidus occurred in the 34th week of pregnancy. Symptoms disappeared completely following premature delivery 2 weeks later. Edema, jaundice and post-partum hemorrhage occurred during the puerpurium.—*D.A.M.*

PASQUALINI, R. Q., AND A. AVOGADRO.

The action of pitressin on thirst in diabetes insipidus. *Rev. Soc. argent. de Biol.* 18: 88. 1942.

Two patients with diabetes insipidus were deprived of water until intense thirst and anxiety developed. The craving disappeared 20 minutes after an injection of 5 units of pitressin. This indicates that the pitressin influences other tissues besides the kidneys perhaps the receptor center of thirst sensation.—*A.E.M.*

VAZQUEZ-LOPEZ, E.

Structures of the neurohypophysis with special reference to nerve endings. *Brain* 65: 1. 1942. *Abst. Arch. Neurol. & Psychiat.* 49: 283. 1943.

This investigation was made chiefly on frozen sections of the pituitary gland of the horse, some studies also being made on the ox, sheep, rabbit, guinea pig and rat. Nerve fibers were stained by silver and gold impregnation methods, to assure differentiation of connective tissue, nerve fibers and neuroglial prolongations. Nerve fibers to the hypophysis arise in hypothalamic nuclei, pass through the eminentia media of the tuber cinereum and enter the stalk in thick, close-set bundles. As they enter the pars nervosa, they fan out and, toward the distal portion, form a dense network of fibers running in all directions. Many of these fibers end in the acellular perivascular spaces formed by the neuroglia around the blood vessels of the neurohypophysis where they form extensive arborizations, including various swellings, clubbings and meniscuses. This profusion of nerve-ending apparatus is rarely equaled elsewhere in the body. A second group of fibers enters the pars intermedia where it appears to come into direct contact with the epithelial cells of the region and to form expansions and other structures, suggesting that nerve fibers end among these cells. Actual pericellular plexuses were not observed. A third group of fibers, in the most distal portion of the gland, form a system of nerve bundles lying beneath the connective tissue capsule of the pars nervosa and end in relation to special meningeal corpuscles which lie embedded in the thick fibrous covering of the apical region. The nerve fibers and nerve endings innervating the meningeal corpuscles are similar morphologically to those ending in the perivascular networks. The meningeal corpuscles appear to have only a sensory function. Furthermore, the morphologic appearance of the nerve endings in the perivascular spaces suggests a close relationship to perivascular nerve endings of a sensory character present in other parts of the body. These facts indicate that the great mass of the neurohypophysis consists of sensory elements and that the main function of the organ must be that of a gigantic perivascular receptive apparatus. Vazquez-Lopez suggests that this sensory system may consist of chemoreceptors and pressoreceptors concerned with regulation of metabolic and hormonal functions. This regulation is mediated through the diencephalic centers in which the nerve fibers to the neurohypophysis originate.—*R.G.H.*

PANCREAS

CRAMER, H. I.

The influence of menstruation on carbohydrate tolerance in diabetes mellitus. *Canad. M. A. J.* 47: 51. 1942.

The author points out that before the days of insulin other observers had noted diminution in carbohydrate tolerance associated with menstruation in diabetic patients. Even in non-diabetics sugar tolerance had been found impaired in the menstrual period. Cases are pointed out in which diabetic acidosis was precipitated when the patient was in the premenstrual or menstrual period. In reviewing the admissions to the Royal Victoria Hospital over a period of years, it was noted that 47.2% of the cases of acidosis without obvious infection or other precipitating causes showed that menstruation had occurred at or about the time acidosis developed. The author then examined 11 menstruating diabetic females and noted the blood sugar before, during and—in some instances—after the menstrual period. Most of the patients failed to show any noteworthy disturbance of the carbohydrate metabolism at the menstrual period although some did show prolonged alteration just before the menstrual period. He concluded that in some diabetics an impairment of carbohydrate tolerance occurs at the menstrual period and that it may be severe enough to precipitate diabetic acidosis. He also concluded that in the same patient this upset may take place in one cycle and not in another.—*J.E.H.*

FISCHER, A. E., AND A. L. FLORMAN.

Transitory hemiplegia associated with hypoglycemia in a diabetic child with congenital heart disease. *Am. J. Dis. Child.* 65: 73. 1943.

An 11 year old girl gave the following picture: (1) congenital heart disease with tetralogy of Fallot; (2) at 9 years, right hemiplegia due to cerebral thrombosis, with recovery after three months; (3) at 11 years, diabetes mellitus for which insulin was required; and (4) an insulin-induced hypoglycemic reaction with a second right hemiplegia, which disappeared when the blood sugar levels were restored to normal. The importance of recognizing similar insulin reactions is emphasized.—*E.C.R., Jr.*

GANEM, J. F.

Influence of folliculin on diabetes. *Rev. méd. de Rosario* 32: 599. 1942.

Estrone, in daily doses of 10,000 to 50,000 I.U., was given intramuscularly to 18 females with moderate diabetes, for periods of 10 to 15 days. There was no effect on glycosuria or hyperglycemia in 9, a decrease in either symptom or a slight decrease in both symptoms in 5, and greatly decreased hyperglycemia and aglycosuria in the remaining 4. The results were similar in pre- and post-menopausal subjects, although in one patient whose diabetes began at menopause the estrone therapy was successful; this is considered as probably coincidental. Estrone is indicated in therapy of diabetes in insulin-refractory females, and a technic of treatment is presented. The only side-effect of estrone noted was insignificant uterine hemorrhage. Its mechanism of action in diabetes is probably through inhibition of the diabetogenic factor of the anterior pituitary.—*Courtesy Biol. Absts.*

GOLDFARB, W., AND M. GOLDEN.

Absorption of carbohydrates in humans. *Proc. Soc. Exper. Biol. and Med.* 51: 134. 1942.

Blood sugar curves after oral ingestion of varying concentrations of glucose were determined. In 30 minutes increase in blood glucose was greater with 5% glucose than with 30% and in patients in insulin coma, recovery was more rapid with the lower concentrations. Intestinal absorption is influenced by relative intestinal and blood glucose concentrations.—*D.A.M.*

KAPLAN, A., C. ENTERMAN AND I. L. CHAIKOFF.

Effects of insulin on the blood lipids of man. *Endocrinology* 32: 247. 1943.

Injection of massive doses of insulin into human subjects failed to alter significantly the blood lipid level. The concentration of free and esterified cholesterol, total fatty acids and phospholipids in the blood were unaffected by the almost complete removal of glucose from the blood stream.—*H.O.H.*

MENKIN, VALY.

Gluconeogenesis and cellular injury. *Am. J. Physiol.* 138: 396. 1943.

An acute inflammation induced in dogs by intrapleural injection of turpentine is accompanied by a marked local glyconeogenesis due to increased proteolysis in the inflammatory area. The excess glucose formed diffuses into the circulation giving rise to hyperglycemia. The experiments support the view that excessive blood glucose levels in diabetics with superimposed infections is due to local protein catabolic processes with gluconeogenesis.—*D.A.M.*

STEINER, M. M., AND P. C. TRACY.

Diabetic coma, acute pancreatitis and bacillus welchii peritonitis. *Am. J. Dis. Child.* 65: 36. 1943.

The following series of events is thought to have occurred in a 13 year old white boy: (1) severe enteritis and duodenitis with changes in the pancreatic ducts; (2) entrance of bile or infected intestinal contents into the pancreas (3) activation of trypsinogen with extensive necrosis of the pancreas including the islet tissue; and (4) onset of fatal diabetic coma with abdominal pain and vomiting, during life thought to be due to the "abdominal syndrome" seen in uncomplicated diabetes, but at post-mortem proven to be due to acute pancreatitis and B. welchii peritonitis. This was the only instance of these complications in 10 autopsied children who had died of diabetic coma at the Children's Memorial Hospital of Chicago from 1921 to 1942.—*E.C.R., Jr.*

VILA, O.

Hexamine-insulin; a clinical study. *Rev. méd. de Rosario* 32: 956. 1942.

Hexamine-insulin, prepared by the addition of methenamine (urotropin) to insulin, has an immediate intense effect and a delayed action lasting for 12 hours. Its effects were tested on rabbits, nondiabetic and diabetic patients. In tests on 15 diabetics, comparison was made with protamine-zinc-insulin, and 7 case reports are cited in detail. A chronology of insulin compounds and mixtures introduced to obtain long duration of hypoglycemic action is included. Hexamine-insulin is considered satisfactory for control of different grades of diabetes.—*Courtesy Biol. Absts.*

PARATHYROID

WERNER, A. D.

Hyperparathyroidism with metastatic deposits in the kidneys, *South M. J.* 35: 671. 1942.

A case is reported of a parathyroid tumor in a 67-year-old woman. The hyperparathyroidism caused by this tumor, which was demonstrated at autopsy, caused marked declacification of the bones, with metastatic deposits of calcium in both kidneys and their pelves.—*H.W.*

THYMUS

TURNBULL, F.

Removal of malignant thymoma in a case of myasthenia gravis. *Arch. Neurol. & Psychiat.* 48: 938. 1942.

A case of myasthenia gravis associated with malignant thymoma is reported. Successful removal of the thymic tumor did not result in any improvement of the myasthenia gravis, as has been reported in some other cases.—*R.G.H.*

THYROID

BARTLETT, W.

Essential biochemical derangements in hyperthyroidism. *Arch. Surg.* 45: 103. 1942.

In hyperthyroidism even with severe increase in symptoms the alkaline reserve of patients remains normal if patients are kept at rest. However, with excretion, the CO_2-combining power of plasma decreases. With improvement of the hyperthyroid state during treatment prior to operation, urinary total acids, organic acids and NH_3 fall and the pH increases. After thyroidectomy, plasma alkaline reserve increases.—*D.A.M.*

DENKER, P. G., AND R. L. OSBORNE.

Aberrant thyroid tumor of the vertebrae with compression of the spinal cord. Recovery after operation and high voltage roentgen therapy. *Arch. Neurol. & Psychiat.* 49: 277. 1943.

A tumor which had involved and partially destroyed the spinous process and laminas of two segments of the thoracic vertebrae of a 27-year-old man was partly removed by surgical operation. It was found to consist of normal thyroid tissue. It was further treated with high-voltage roentgen rays. Follow-up observations after 10 years revealed complete recovery. Review of the literature failed to disclose any similar case of benign metastatic thyroid lesion of the spine with complete recovery.—*R.G.H.*

FOTHERINGHAM, W. TEJERINA.

Recurrent hyperthyroidism. Postoperative persistence or relapse. *Rev. méd. de Rosario* 32: 819. 1942.

The etiology is discussed and 4 case reports are cited. Three had persistent hyperthyroidism after sub-total thyroidectomy, and 1 relapsed. Two of the 3 were cured by re-operation. The patient who relapsed following the first thyroidectomy was again operated, but so recently that the permanence of cure cannot be judged. Results at the Lahey Clinic showed 9.2% of 306 patients with recurrent hyperthyroidism presented symptoms of hyperthyroidism after re-operation.—*Courtesy Biol. Absts.*

FOURNIER, J. C. M., AND J. M. CERVINO.

Congenital myxedema without mental disturbance. *Arch. urug. de med., cir. y especialid* 20: 93. 1942.

The authors discuss an unusual case of congenital myxedema. The symptoms probably became obvious during the third year. At the age of 10, thyroid treatment was begun. The singularity of this case was the fact that although the usual physical disturbances and retardations had taken place, the mental age was normal.—*Courtesy Biol. Absts.*

KOBACKER, J. L.

Production of goiter and myxedema by thiocyanates. *Ohio State M. J.* 38: 541. 1942.

Treatment for hypertension of a 48-year-old woman, who previously had a moderate diffuse thyroid fullness, with potassium thiocyanate for a period of 17 months, led to myxedematous goiter with a B.M.R. of −30. Omission of thiocyanate and thyroid therapy brought about return to a normal state in 2 months. KCNS therapy a year later induced a mild degree of myxedema.—*D.A.M.*

STEWART, H. J. AND W. F. EVANS.

Periferal blood flow in myxedema. *Arch. Int. Med.* 69: 808. 1942.

Periferal blood flow in 6 patients with myxedema decreased in proportion to the reduction in B.M.R. Following thyroid therapy, periferal blood flow and cardiac output increased with improvement in clinical conditions.—*D.A.M.*

TROTTER, W. R., AND N. WALLACE.

Thyroxine in myxedema. *Brit. M. J.* 1: 183. 1942.

A patient who could not tolerate oral thyroid because of vomiting was treated satisfactorily with intravenous thyroxine, 7.5 mg. every 4 weeks.—*D.A.M.*